Chapter

Lung Cancer Oncotherapy through Novel Modalities: Gas Plasma and Nanoparticle Technologies

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Abstract

Cold atmospheric pressure plasma (CAP) is emerging as new healthcare technology and it has a high potential through physical and chemical effects for cancer treatment. Recently, CAP, plasma activated liquid (PAL), and nanomaterial have been significant advances in oncotherapy. Reactive oxygen-nitrogen species (RONS), electrical field, and other agents generated by CAP interact with cells and induce selective responses between the malignant and normal cells. Nanomedicine enhances therapeutic effectiveness and decreases the side effects of traditional treatments due to their target delivery and dispersion in tumor tissue. There are various nanocarriers (NCs) which based on their properties can be used for the delivery of different agents. The combination of gas plasma and nanomaterials technologies is a new multimodal treatment in cancer treatment, therefore, is expected that the conjunction of these technologies addresses many of the oncology challenges. This chapter provides a framework for current research of NC and gas plasma therapies for lung cancer. Herein, we focus on the application of gas plasmas and nanotechnology to drug and gene delivery and highlight several outcomes of its. The types and features of the mentioned therapeutics strategy as novel classes for treating lung cancer individually and synergistic were examined.

Keywords: gas plasma, nanocarrier, reactive oxygen and nitrogen species (RONS), selectivity, lung cancer

1. Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide, with a survival of only 15% of cancer patients 5 years after diagnosis. Eighty-five percent of lung cancers are classified as non-small lung cells, including adenocarcinoma (ADC), squamous cell carcinoma (SCC), and large cell cancer, with 75% being diagnosed in advanced stages [1].

Due to the failure of common chemotherapeutic agents, resistance to them in lung cancer patients, and given the high mortality rate of this type of cancer, urgent need for new therapies that overcome drug resistance [2]. Alternative treatments must have fewer side effects and are more effective.

Gas plasma is a cocktail of chemical and physical factors including short and long-lived RONS, ions, electrons, UV photons, and electric fields. One of the important practical applications of plasmas lies in the future, in the field of

medicine. Plasma medicine is an emerging strategy for widespread applications such as oncotherapy, wound healing, virology, biofilm, implant surfaces, and dentistry [3]. Plasma oncology that uses gas plasma technology for cancer treatment, is one of the newest and most promising multimodal therapies in cancer treatment [4]. Cancer treatment by plasma in two methods direct exposure and plasma-activated liquid (PAL) in the form of in vitro and in vivo have developed and had an impressive effect [5]. Responses of cancer cells to CAP respectively from 2004 to 2019, are apoptosis, growth inhibition, cytoskeletal damage, selective cancer cell death, cell cycle arrest, DNA, mitochondrial damage, growth inhibition in vivo, increased intracellular ROS, a selective increase of ROS, immunogenic cancer cell death, cell-based H_2O_2 generation, and currently, selectivity mechanism based on primary and secondary singlet oxygen [6].

Multimodal or combination cancer therapies can provide better treatment outcomes for patients. CAP can be used as a novel method because it combines electromagnetic, chemical, and thermal compounds in mild doses. It also combines well with other methods to produce beneficial synergistic effects [7].

Advances in nanotechnology have led to the rapid development of the synthesis, characterization, and application of nanocarriers (NCs) in cancer treatment [8]. Nanomaterials, due to their unique properties, can provide benefits such as clinical diagnosis, heat treatment, and body imaging, so they are a good candidate for pharmaceutical systems. One of the most important advantages associated with NC systems is their ability to withstand physiological stress or improve biological stability and their oral consumption, which makes them more attractive than other delivery strategies [9]. To be several innovative drug delivery methods are used in cancer treatment. A wide range of nanocomposites based on synthetic polymers, proteins, lipids, and organic and inorganic particles have been used to treat cancer specifically to deliver drugs specifically to solid tumors. A carrier offers many benefits such as protection against damage to the bloodstream, better drug solubility, increased drug stability, targeted drug delivery, reduction of toxic effects, and drug improvement. Permeability and preservation of the enhanced effect have long been considered as the main mechanism to facilitate the preferential accumulation of nanoparticles in tumor tissues compared to normal tissues [8–10].

CAP and nanoparticles have been known that alone or simultaneous with conventional therapies to covers wide ranges of oncotherapies challenges. There are interesting similarities and contrasts in their interaction with living cells and tissues, and these are directly related to the characteristics and scope of their therapeutic modality, especially chemical reactivity, selective action against pathogens and cancer cells, immunity to healthy cells and tissues, and transmission. It is time to consider synergies and the simultaneous combination of plasma-nanoparticles and their associated benefits for the development of effective therapies that improved selective efficacy and high safety for modern medicine. Here, a detailed overview of the advantages and limitations of nanomedicine and plasma medicine as novel technologies are presented and then we enumerate some of the main possibilities of synergy between nanotechnology and plasma technology for lung cancer treatment [11–14].

2. Gas plasma as an oncotherapeutics agent

2.1 Definition and application of gas plasma

Gas (also known as physical) plasma is the fourth state of matter and represents a quasi-neutral gas of charged and neutral particles that exhibits collective behavior. The plasma is categorized into three types of hot, warm, and non-thermal

(cold) plasmas [15]. CAP has recently become a promising solution to a range of challenges due to its diverse applications in healthcare, environmental remediation and pollution control, materials processing, electrochemistry, nanomaterial synthesis, and more have been considered [16]. Cold (non-thermal) plasma is a cocktail of chemical and physical agents such as short-lived reactive species, long-lived reactive species, electromagnetic field, and ultraviolet radiation [17]. Plasma treatment is transferring of these reactive agents to targets or samples. Generation, interaction and transferring of reactive agents from plasma to the target as shown in **Figure 1**, contains multidisciplinary areas including plasma physics, plasma chemistry, solution chemistry, and biochemistry [18].

These reactive agents cause the plasma to have promising biological effects. Gas plasma as an emerging therapeutic implication has attracted attention recently in various fields of medicine. Cancer treatment, wound healing, dental hygiene, bacteria eradication, and blood coagulation are some of the promising fields for plasma treatment [17]. When CAP devices for cancer application are developed and optimized plasma sources, biologically relevant plasma components, physical and chemical characterization, and application adapted designed are the most important aspects before in vivo and clinical application that should be considered [19].

On the other hand, a mixture of specific factors including device parameters (treatment area, flow rate, working gas, gas composition, shielding for tuning), process parameters (treatment time, incubation time, direct vs. indirect, distance to effluent, throughput), cell type (normal vs. cancer), morphology and physiology, surface receptor expression, volume and content of liquids, chemical composition of liquids, physiological state and disease, and penetration depth influencing the impact and efficiency of gas plasma performance [20].

Redox flux increase to cells, multimodality nature, mild effect, flexibility in use, and dose-dependent effect as primary features of CAP cause to unique clinical properties of plasma including selectivity for cancer cells, enhancing cancer chemosensitivity, stimulation of the immune system, elimination of cancer stem cells, and halting cancer metastasis [3].

2.2 Selectivity mechanism of CAP and PAM

The inefficacy of utilized approaches in oncotherapy has turned cancer into a chronic disease. Conventional anti-cancer agents lack the selectivity towards normal and cancer cells and target over than malignant tumors. Targeting normal cells and pathways that are necessary for the survival of its limited application of common modalities. As a result, new oncotherapeutics strategies must have high selectivity performance [8, 14].

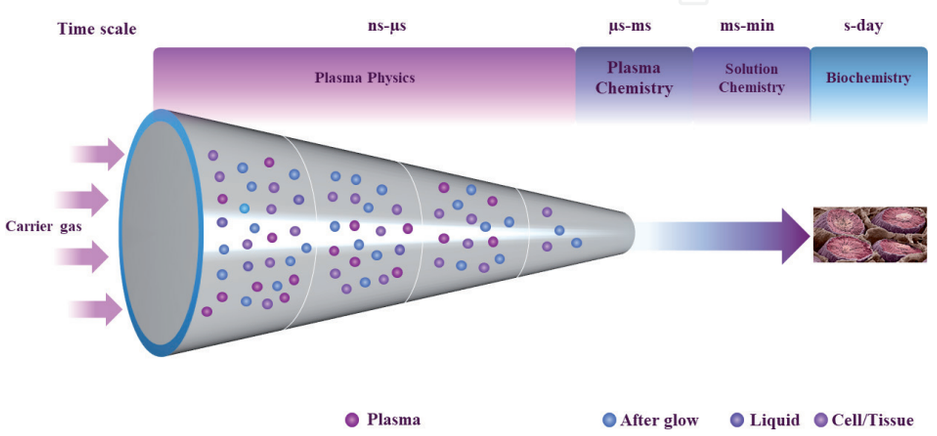

Figure 1.
Generation, interaction and transferring of reactive agents from plasma to the biological target.

Possible mechanisms that have been proposed for selective effects are based on the fundamental difference between normal and cancer cells. In contrast to normal cells that do not metabolize glucose for lactation in the presence of oxygen, cancer cells have different and abnormal metabolism and even metabolize glucose for lactation in the presence of oxygen (aerobic glycolysis). This effect, known as the Warburg effect, is one of the most important metabolic differences in normal and cancerous cells. Therefore, cancer cells are more sensitive to the accumulation of ROS than normal cells [21]. The ROS play a key role in conventional cancer treatments such as chemotherapy and radiation therapy. Among them, hydrogen peroxide can be considered as the most basic and important species [22]. Cold plasma is also being integrated with the production of RONS in the context of therapeutic methods based on redox reactions. Nevertheless, despite the similarities at least in the level of reactive oxygen species between the mechanism of CAP and other anticancer drugs, CAP by generating RNS distinguishes itself from other treatments [23].

The selectivity mechanism of CAP and PAM between the normal and cancerous cells has been discussed in previous studies. Several factors influence the selective effect of CAP and PAM, such as the expression of aquaporins or cholesterol or the ability to protect against oxidative stress by the anti-oxidative system to determine how many RONS can enter the cell and interfere with intracellular signaling pathways. Bauer and Graves in recent years suggested that activation of intercellular Hypochlorous acid (HOCl) signaling which after catalase inactivation through subsequent generate primary and secondary $^1O_2$ by the interaction of long-lived species in PAM have a key role in the selectivity of CAP and PAM [24, 25]. Keidar and colleagues proposed that the key role in selectivity for expression of aquaporin levels and suggested that the high level of aquaporin that makes the more hydrogen peroxide (H_2O_2) derived plasma as a key anticancer RONS, penetrates the cell and initiate apoptosis. In other words, cancer cells are more vulnerable than normal cells due to the high expression of aquaporin on cytoplasmic membranes [26, 27]. Van der Paal et al. suggested that RONS enter into normal and cancer cells according to the corresponding cholesterol fraction of their cell membrane. Since cancer cells have lower cholesterol fraction compared to normal cells, they are most affected [28, 29]. Despite all the studies that have been done, the selectivity of CAP and PAM is still a matter of scientific debate and there is no consensus in the community.

Bauer et al. have recently presented a mechanism for selectivity of CAP and PAM that includes three steps. The generation of primary and secondary singlet oxygen which is inactivated membrane-associated catalase (step1), penetration of H_2O_2 through aquaporins (step2), and at the final step causes cell death through the mitochondrial pathway of apoptosis by the reactivated HOCl or $^{\bullet}NO/ONOO^-$ – mediated apoptosis-inducing signaling. $^1O_2$, which can be considered an important role in the selectivity of CAP and PAM, is produced primarily from hydrogen peroxide and nitrite that are two long-lived species in PAM, and in the second stage, $^1O_2$ is generated from H_2O_2 and $ONOO^-$ due to NOX1 (membrane) and NOS (intracellular) respectively (**Figure 2**) [24, 25, 30, 31].

2.3 Gas plasma for lung cancer oncotherapy

Even though a concise time has been passed since the initial discovery of plasma oncotherapy, we are seeing tremendous progress in this field, and day to day the hope of becoming a treatment option for clinical practice is increasing. The effect of gas plasma on all types of cancer including oral cancer, hepatic cancer, skin cancer, glioblastoma, breast cancer, pancreatic cancer, ovarian cancer, neuroblastoma,

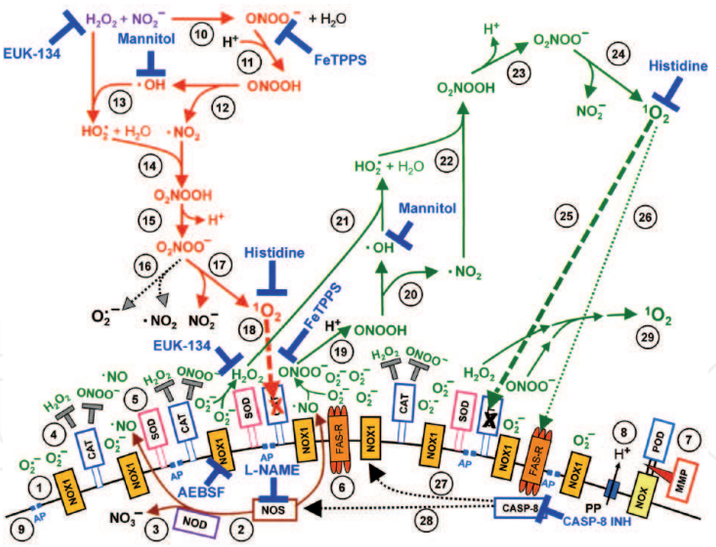

Figure 2.
Apoptosis induction by CAP/PAM is mediated by the generation of primary and secondary singlet oxygen ($^1O_2$). NADPH oxidase 1 (NOX1) is expressed in the membrane of tumor cells and generates extracellular superoxide anions ($O_2^{\bullet-}$) (#1). NO synthase (NOS) (#2) generates $^{\bullet}NO$ which can be either oxidated by $^{\bullet}NO$ dioxygenase (NOD) (#3) or pass through the cell membrane. Membrane-associated catalase (#4) protects tumor cells towards intercellular RONS-mediated signaling. Comodulatory SOD (#5) is required to prevent $O_2^{\bullet-}$- mediated inhibition of catalase. Further important elements in the membrane are the FAS receptor (#6), dual oxidase (DUOX) (#7), from which a peroxidase domain (POD) is split through matrix metalloprotease, proton pumps (#8) and aquaporins (#9). H_2O_2 and NO_2^- derived from CAP treatment and stable in PAM interact and generate peroxynitrite ($ONOO^-$) (#10). In the vicinity to membrane-associated proton pumps $ONOO^-$ is protonated to peroxynitrous acid (ONOOH) (#11) and decomposes into $^{\bullet}NO_2$ and $^{\bullet}OH$ radicals (#12). $^{\bullet}OH$ radicals react with H_2O_2, resulting in the formation of hydroyperoxyl radicals ($HO_2^{\bullet}$) (#13). The subsequent generation of peroxynitric acid (O_2NOOH) (#14) and peroxynitrate (O_2NOO^-) (#15) allows for the generation of "primary singlet oxygen" ($^1O_2$) (#17). Primary $^1O_2$ causes local inactivation of membrane-associated catalase (#18). Surviving H_2O_2 and $ONOO^-$ at the site of inactivated catalase are the source for sustained generation of "secondary $^1O_2$" through reactions #19- #24. Secondary $^1O_2$ may either inactivate further catalase molecules (#25) and thus trigger autoamplification of $^1O_2$ generation (#29), or activate the FAS receptor (#26) and in this way enhance the activities of NOX1 and NOS. This enhances the efficiency of secondary $^1O_2$ generation. The site of action of specific inhibitors and scavengers are indicated. Please find details on the elements on the surface of tumor cells in ref.s, on singlet oxygen generation in ref.s, and on intercellular apoptosis-inducing signaling after catalase inactivation in ref.s. this figure was obtained with permission from [25] under the terms of creative commons CC BY license.

prostate cancer, head and neck cancer, lung cancer, osteosarcoma, leukemia, and colorectal cancer have been studied at least in in-vitro levels. The volume of work has expanded greatly in recent years and has even expanded to the evaluation stage of plausible action mechanism of plasma, which was described in detail in the previous section. Another factor that has led to great hope in this field is the apparent success of plasma for a wide range of cancers. In particular, enhancing chemosensitivity and selectivity respecting to cancer cells of plasma in comparison to routinely treatments were remarkable achievements for plasma.

Lung cancer treatment studies approximately include 10% of plasma oncology research. Although most studies still are limited to laboratory and animal work, the initial outcomes show high plasma potential for the treatment of lung cancer. In this section, in addition to reviewing the studies, we enumerate the limitations and try to enumerate some of the possibilities of future work. Here, we review all of the current research on lung cancer treatment by CAP.

2.3.1 The impact of plasma device and process parameters on lung cancer cells

The nature of plasma is such that the cocktail of plasma device parameters affects the oxidation potential and its performance when interacting with the

target [32]. **Figure 3** is documented depicts a set of all the factors that are important for plasma therapy. If it is still unknown to us how chemical and physical factors affect target or sample, but in general it can be said that all the factors mentioned in the figure, affect plasma-target interaction. However, it is impossible to explain explicitly these issues, especially the plasma dose is a debate for plasma medicine society.

Lung cancer also has been evaluated by a variety of plasma oncology factors. Preliminary works only examining the effects of plasma device and process parameters including working gas, flow rate, applied voltage, frequency, and treatment time. Therefore, the authors try to investigate the effects of the physical factors of different plasma devices on cancer cells and only evaluated the cell death and did not study to determine the molecular mechanism of CAP.

Huang et al. attempt to evaluate the efficiency of gas plasma on lung cancer cell lines. Device and process parameters such as increasing applied power and prolonging exposure time, respectively, influence the efficiency of gas plasma on A549 cancer cells. In addition, introduced OH, O, N_2, N^+, Ar, Ar^+, and Ar^{2+} radicals that generated with plasma as responsible for cell deactivation [33].

Akhlaghi et al. more focused on device parameters and examine the effects of the gas mixture, gas flow rate, applied voltage, and distance from the nozzle on the two lung cancer cell lines. 3 T3 cell line related to the fibroblast was also evaluated. The authors argue that except for the gas flow rate other mentioned parameters can affect the efficacy of plasma. In particular, treatment time plays a decisive role in the viability of cancer and normal cells [34].

A549 lung cancer cells evaluated with mDBD plasma. Karki et al. believe that mDBD plasma can localized target lung cancer. Also, the cell culture medium temperature did not exceed 26°C. The production of reactive oxygen and nitrogen species inhibits cell migration and is thought to be the main factor in the plasma process and induces apoptosis in lung cancer cells [35].

Various plasma devices have been used to treat lung cancer. Most of these devices are made by the research teams themselves and rarely meet the required standards for medical devices. Details of the multiple plasma devices used for lung cancer are summarized in **Table 1**.

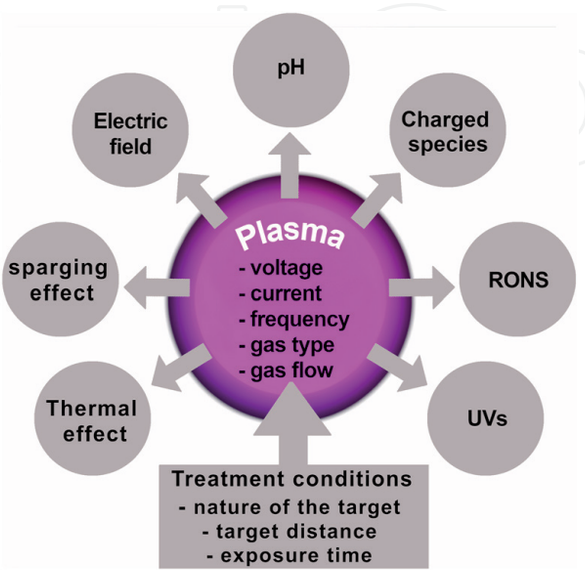

Figure 3.
The interaction between CAP and the treated target. This figure was obtained with permission from [32] under the terms of creative commons CC BY license.

Device	Type	Gas	Voltage (kV)	Frequency (kHz)	Treatment time (min)	Distance (cm)	Slm	Ref
Microplasma	Jet	He	6–9	32	0.03–0.33	1	0.01–0.1	[36]
Plasma jet	Jet	He	2–5	n.a	0.5	1	11	[37]
NTP device	DBD	He	12	24	1–3	0.5	1.33	[38]
Plasma needle	Jet	Ar	30	11.55	0–6	n.a	0.9	[33]
Plasma jet	Jet	He/O_2	1.8	50	0.16	0.5	0.5	[39]
mDBD plasma	Jet	Air	12	1	0–2	0.1	n.a	[40]
APPJ	Jet	He	7	39.5	0–0.5	n.a	1	[41]
CAP device	Jet	He	8	25	n.a	2	4	[42]
NTAPPJ	Jet	Ar	4	19.5	0–2	1.4	3	[43]
NEAPP	DBD	Ar	10	0.06	3	0.3	2	[44]
Plasma device	DBD	Air	0.08	0.06	0–5	0.4	n.a	[45]
APPJ	Jet	He	0.7–1.1	35	0.16	1	0.1	[46]

Table 1.
Overview detail of plasma devices for lung cancer oncotherapy.

2.3.2 The selective effects of gas plasma oncotherapy towards lungs normal and cancer cells

Followed by the initial studies, plasma oncology research continued with the addition of healthy cells. With the addition of normal cells, the selective effect of gas plasma oncotherapy was added to the set of plasma oncology studies. Lung cancer, as one of the most challenging cancers, was one of these cancers on which the selective effect of plasma was investigated. Here is a review of several works that were placed in this category.

In a highly interesting work, Keidar et al. examined the selective effects of cold plasma in vitro and in vivo on different types of cancer. That study demonstrated the selective effect of cold plasma on the normal human bronchial epithelial (NHBE) and lung cancer (SW900) cell lines. Beyond negligible thermal effects of plasma therapy, their study suggests cell adhesion, cell proliferation, growth regulation, and cell death in cancer processes, are selectively deregulated by non-thermal plasma modality. Besides, the possibility of improved survival, reductions in tumor volumes, and paradigm shift in cancer therapy through cold plasma treatment were reported for the first time in this study [37].

Kim et al. to investigate the influence of cold plasma on TC-1 mouse lung carcinoma cells (ATCC No. JHU-1) and mouse fibroblast CL.7 cells (ATCC TIB-80), developed a highly flexible microplasma jet device comprising hollow-core optical fibers of three different sizes. Under different experimental conditions, plasma induce dose-dependent apoptosis and did not affect a necrotic response in the cultured cells. Also, plasma plume size is a dominant factor in the efficacy of plasma. On the other hand, TC-1 tumor cells were more sensitive to plasma exposure than CL.7 fibroblast cells under these experimental conditions. Therefore, under these plasma dose conditions, plasma oncology can be used as a selective treatment for TC-1 tumor cells with no harm to CL.7 fibroblast cells [36].

A previous study also has reported selectivity of gas plasma towards normal (BEAS-2B, HEK293T) and cancer (A549) cells. The generation of intracellular reactive oxygen species (ROS) in cancer cells is higher than in normal cells and this difference is the main cause for the selectivity of gas plasma oncotherapy [46].

2.3.3 Plasma activated liquid for lung cancer treatment

On the other hand, in recent years, due to some limitations of direct plasma treatment such as the inability to penetrate the tissue, maintenance problems, etc. A new type of plasma therapy in the form of the plasma-activated liquid has developed. Exposure of liquids (medium, water, PBS, and ...) to plasma plume and add these activating liquids to the biological samples or living tissue recently received attention as a plasma treatment modality [47]. As adjuvant oncotherapy, Cheng et al. used plasma activated medium (PAM) for investigating the impact of gas plasma on benign mesothelial cells, CL1–5 and A549, normal fibroblasts, and cancer-associated fibroblasts (CAFs) cells. To evaluate PAM as a treatment method that can be used in clinical applications, its effectiveness was compared with hyperthermochemotherapy. This study revealed PAM selectively inhibits the proliferation of lung cancer cells and these effects are related to the produced H_2O_2 and NO_2^- in the culture medium [43].

Another study in this regard has dealt in detail with the various interactions and factors affecting the process of plasma therapy. An important role of the composition of culture medium and maintainability of activated medium for at least one week in −80 C are some of the interesting results of this study. PAM accompanied by ER stress induces caspase-independent apoptosis in A549 lung cancer cells through down-regulated anti-apoptosis proteins, activating PARP-1, and AIF release. H_2O_2 as a long live reactive oxygen species plays an important role in the whole process of plasma therapy [44].

The last literature regarding the application of PAM for lung cancer was done by Kumar et al. The temperature and pH culture medium not changed significantly after activating via discharge. The concentration of H_2O_2 as a key indicator at the different numbers of pulsed plasma discharge was measured. It was observed that lung cancer cells were more susceptible to PAM and PAM selectivity induces apoptosis in lung cancer cells [48].

2.3.4 The underlying molecular mechanism induced by gas plasma in lung cancer

Recently, studies in this field have entered a new arena and in some cases, mechanism of action also study. In recent years, with the expansion of the understanding of plasma redox research, has entered a new phase and the mechanism of plasma function with a focus on RONS, as determining factors in the treatment process are evaluated. Herein, we discuss the role of generated RONS by CAP. It can be seen that plasma has appeared successful in more studies and has been able to selectively induce apoptosis in cancer cells.

A noteworthy study by Yang et al. has investigated the molecular mechanism of gas plasma effects on A549 and H1299 cells. The most striking result to emerge from the data is that miR-203a/BIRC5 axis was affected by gas plasma. The miR-203a targets BIRC5 which plays a critical role in angiogenesis, proliferation, and regulating the cell cycle in cancer cells. Therefore, Gas plasma with upregulation miR-203a suppressed proliferation and promoted apoptosis in A549 and H1299 cells [41].

Ma et al. evaluated the effects of gas plasma and the contribution of reactive oxygen and nitrogen and plausible molecular mechanism on human lung adenocarcinoma epithelial (A549). Due to cell types and different plasma doses, they conclude that various cell types indicated different sensitivity under plasma

irradiation. Although H_2O_2 has a vital role but other ROS or RNS such as NO_3^-, $HO^•$, etc. generated by plasma also be involved in the mechanism of it. Plasma induces cell death, apoptosis, DNA damage, and mitochondrial dysfunction and these are related to generated reactive species in the culture medium. Although CAP and PAM exhibit similar performance at low doses, at high doses PAM exhibits less toxicity compared to CAP [38].

Along with the physical characterization, the molecular mechanism of plasma on human lung adenocarcinoma cell lines (A549) was examined by Joh et al. Besides, the flow rate and working gas mixture in detail evaluated. This study provides new insights into the physical characterization of gas plasma. The over-production of ROS induces DNA damage accompanied with high expression of p53 [39].

Karki et al. utilized 3D collagen matrices to assess apoptotic cell death of A549 lung cancer cells by applying gas plasma. They found generated reactive oxygen and nitrogen species reduces the viability of A549 lung cancer cells. Gas plasma has a greater impact on the superficial surface of 3D matrices but by penetrating deep into the 3D matrix, its effect is reduced [40].

The last work of this group explored the selective effect of gas plasma onco-therapy on both A549 as lung adenocarcinoma and MRC-5 as lung fibroblast cells. Besides, the extracellular concentration of reactive oxygen and nitrogen, cell cycle analysis, and the expression of genes related to apoptosis were investigated. Although gas plasma significantly targets cancer cells, the viability of normal cells is also reduced. Cancer cells in comparison to normal cells had higher expression of apoptosis-related genes (H2AX, BAX, 53, Caspase-8, and ATM) and greater penetrated intracellular RONS [49].

The most interesting finding of another study is related to the potential mecha-nism of gas plasma on A549 cells. The authors utilize the microarray approach in detail to examine the cellular response to stress, cell cycle, apoptotic process, and other cellular functions response to plasma irradiation for the first time. The author concluded changes in MEKK, GADD, FOS, and JUN gene expression that causes p53 and mitogen-activated protein kinase (MAPK) signaling pathways activation. From the results related to the expression of related genes cellular differentiation and proliferation also was observed [50].

The basic contention of Panngom et al. which was obtained from a study on H460 and HCC1588 (human lung cancer cell lines) and two human lung normal cell lines (MRC5 and L132) is that Gas plasma can preferentially kill cancerous lung cancer cells. Data from apoptosis-related assays consistent with cell death revealed H460 cancer cells more affected in comparison to MRC5 normal cells by plasma treatment. In the shorter treatment time, plasma selectively targets cancer cells and normal cells are not affected but at the longer plasma exposure time, the viability of two cancer and normal cells approximately equally reduces. The core finding of this work introduces a new strategy for lung cancer treatment through mitochondria targeting. On the other hand, although, they point to the possibility of intrinsic and extrinsic apoptosis pathways, they emphasize mitochondria-mediated apoptosis [45]. Finally, according to Ma et al. Heme oxygenase-1 (HO-1) as a target could be considered for the future oncotherapeutics modalities. This exciting result comes from that gas plasma via generation of ROS inhibits Nrf2/HO-1 pathway in A549 cells [51].

3. Nanoparticle based delivery system for lung cancer treatment

The term nanotechnology describes a wide range of nanometer-scale tech-nologies with widespread applications in various medical and industrial areas.

Nanotechnology involves the production and application of physical, chemical, and biological systems at scales ranging from individual atoms or molecules to about 100 nanometers, as well as the integration of resulting nanostructures into larger systems [9]. Now, the convergence of disciplines (chemistry, biology, electronics, physics, engineering, etc.) has led to multiple applications in the treatment of diseases including cancer, the production of materials, computer chips, medical diagnostics, and healthcare, energy, biotechnology, space exploration, and security issues. Therefore, nanotechnology is expected to have a significant impact on our economy and society over the next 10 to 15 years, and to become more important in the long run as more scientific and technological advances are made. It is the convergence of science on the one hand and the growing diversity of applications on the other that is advancing the potential of nanotechnologies. In fact, their greatest impact may come from an unexpected combination of previously separate aspects [10].

Drug delivery in nanoscale with advances in nanotechnology has had an impressive effect on clinical therapeutics in comparison with conventional chemotherapy in the last two decades. NCs have made from different materials such as organic nanocarriers, inorganic nanocarriers, and a combination of both as shown in the composition section of **Figure 4**. Lipid-based nanocarriers and polymeric frameworks are known as organic nanocarriers, while quantum dots and silica nanoparticles are inorganic nanocarriers [52, 53].

Nanotechnology is a science for the production of carriers at a nanometer scale, and Nanomedicine is an important field of academic research causing clinical and commercial development. NCs must have certain properties to be efficiently transmitted; 1) because they are used in this method for delivery of drugs to specific targets and cells, for decreasing side effects and damaging impact on normal cells should have a specific antibody on their surface that binds to a specific marker on cancer cells as shown in targeting section of **Figure 4** [54], 2) NCs should not arouse the immune system, to prevent of their degradable before receiving by tumor cells [55], 3) and the entrance of NCs into solid tumors and release of agents based on the characteristic of NCs and cancer cell.

Drug release is controlled by many external and internal stimuli, e.g. temperature, pH, ionic strength, sound, redox, and electric or magnetic fields that improve the targeted therapy [56]. Good biocompatibility, low toxicity, high stability, size, shape and surface charge of NCs have a crucial role in their biological performance. There are various methods for preparing NCs, agents can encapsulate in the matrix or the core of NCs and also in some cases can chemically bind to the surface of NCs [57].

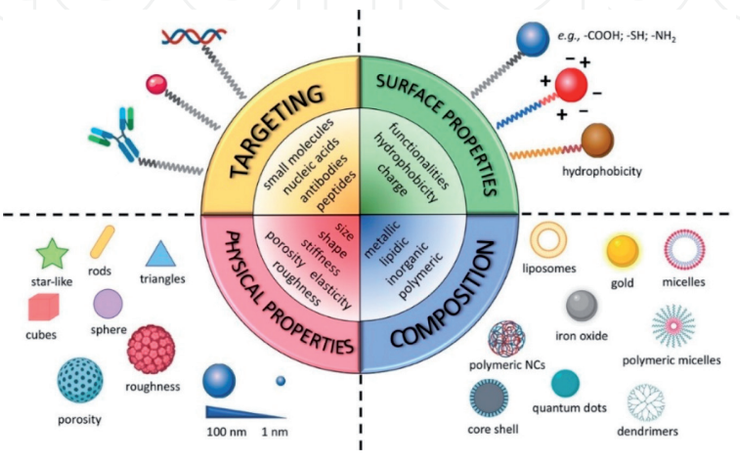

Figure 4.
Physical and chemical properties of nanocarriers. This figure was obtained with permission from [52] under the terms of creative commons CC BY license.

Gene delivery along with drug delivery is used for cancer treatment. Increase the production of some proteins or downregulation (or silencing) of some genes with the use of antisense or siRNA are the basis of this treatment. Low toxicity is the dedicated property of this type of therapy [58].

In this section, we have classified a few numbers of performed research for lung cancer treatment based on their type of NC. Most of these studies have been implemented in the level of in vitro and in vivo and evaluating cellular uptake, cytotoxicity, apoptosis, volume and growth of tumors. From my point of view, some of them have the potential to enter the clinical trial phase. For some of them is necessary to study more about the drugs and nanocarriers action mechanism in tumor tissue, which should be further studied.

3.1 Organic nanocarriers

3.1.1 Lipid-based nanocarriers

Recently lipids are very popular systems for the delivery of drugs to target tissues. There are different types of lipids, that use in this drug delivery system such as oils, waxes, cholesterol, sterols, triglycerides, phospholipids and fat soluble vitamins. Lipid-based NCs due to the electrostatic interaction between the polar phospholipid head and the solvent have spherical shape. The flexible nature of lipid-based NCs like liposomes helps them to squeeze large particles into small intercellular pores. Neutral surface charge of nanoparticles causing their Instability. The inside surface of blood vessels and cells contains many negatively charged components such as glycocalyx, so Lipid-based NCs surface charge is designed positive for better absorption to target cells [59, 60].

Some of the studies that use lipid-based NCs gathered below, for comparison the level of the studies and effectiveness of different types of lipid-based NCs in recent years. A549 cells are the most usable cells for in vitro and in vitro (A549 tumor-bearing mice) experiments that are treated with different kinds of drugs and agents conjugated with lipid-based NCs. An increase in cellular uptake, cytotoxicity and apoptosis and a decrease in tumor growth and volume were the most common results obtained from in vitro and in vivo experiments respectively.

In 2018 Kabary et al. produced layer-by-layer (LbL) lipid nanoparticles (NPs) by lactoferrin (LF) and hyaluronic acid (HA) to deliver berberine (BER) and rapamycin (RAP) for the treatment of lung cancer. NPs with capsulated agents increase cytotoxicity against A549 lung cancer cells by rising up the entrance of drugs to the cells. Drug release was controlled by binding BER to sodium lauryl sulfate (SLS) and production of BER-hydrophobic ion pair (BER-HIP). LF and HA on the surface of lipid NPs caused the stability of them. These NPs protected RAP against hydrolysis and augment its stability in phosphate buffered saline (PBS). In vivo experiments also indicate the growth of tumor was inhibited, and RAP can decrease the angiogenesis by inhibiting vascular endothelial growth factor (VEGF) and BER has an inhibition effect on angiogenesis and tumor progression via blocking of various pro-inflammatory and angiogenic factors. To mice fed HA/LF-LbL-RAP-BER/SLS-NPs, the level of Ki-67 as a proliferation marker was reduced in tumors in comparison with control [61].

Overexpression of nuclear factor E2–related factor 2 (Nrf2) caused drug resistance in lung cancer. Therefore, in other research, hyaluronic acid-based nanostructured lipid carriers (NLCs) for specific targeting via CD44 receptor in cancer cells was used to increase the effect of apigenin (APG) as an Nrf2 inhibitor. After treatment of A549 cells with this NC, cells became sensitive to docetaxel (DTX) and cell toxicity increased. HA-APG-NLCs also induced apoptosis in treated A549 cells (**Figure 5**) [62].

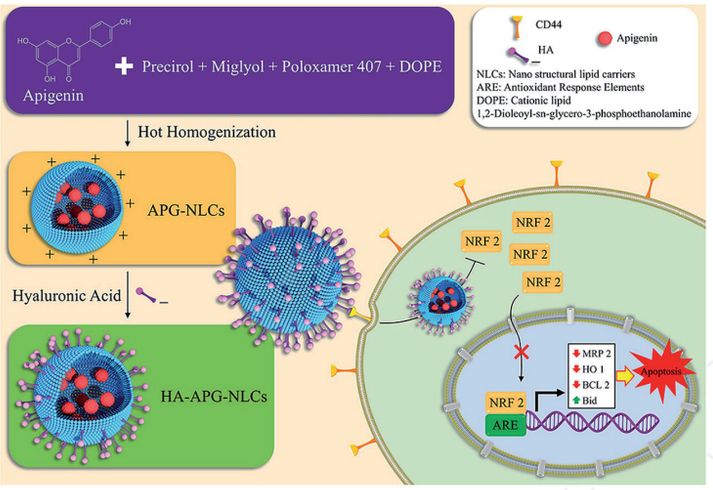

Figure 5.
Schematic of targeted hyaluronic acid-based lipid nanoparticle for delivery of apigenin in lung cancer cells. This figure was obtained with permission from [62] under the terms of creative commons CC BY license.

Also in 2019, Cetuximab (CET), paclitaxel (PTX) and 5-Demethylnobiletin (DMN) conjugated to nano lipid carriers (NLCs) (CET-PTX/DMN-NLCs). A549 cell viability after treatment by CET-PTX/DMN-NLCs decreased, and the anti-tumor effect was evaluated by in vivo experiment on Lung tumor xenografts mice [63].

Moreover, EGFR-targeted lipid polymeric nanoparticles (LPNs) conjugated to EGF-PEG-DSPE ligand in the outer layer and encapsulated cisplatin (CDDP) and doxorubicin (DOX) in the core and phospholipid layer respectively. While this nanocarrier reaches to target tissue DOX released faster than CDDP. Cytotoxicity showed a dose-dependent manner in this study. Accumulation in the heart and kidney are very lower than tumor tissue, and tumor volume and growth decreased significantly after treatment [64].

Wang and colleagues used Tf modified redox-sensitive lipid-polymer hybrid nanoparticles enclosed Afatinib (Afa) (Tf-SS-Afa-LPNs). There is a positive relation between GSH concentration and drug release. Cell proliferation was inhibited after treatment by Tf-SS-Afa-LPNs, and in vivo experiments showed afatinib accumulate more in the lung and lead to antitumor activity in it [65].

According to a recent report in 2020, for treatment of small-cell lung cancer (SCLC) polyphenol curcumin (Cc) as a natural drug bind to polysaccharide-cloaked lipidic nanocarriers (Cc@CLNs). This nanocarrier has some properties that stand out it from others: potential of penetration to the cell membrane, resistance to degradation of pepsin and trypsin, increase cellular uptake and bioavailability. Absorption of Cc@CLNs was analyzed by in situ experiments in rats and results showed uptake increased through Cc@CLNs compared with free Cc. For in vitro experiment H446 cells were cultured, the viability of cells showed time- and dose-dependent behavior. Cc@CLNs induced cell apoptosis and also augment the value of the intracellular ROS. Also, Cc@CLNs causing a decrease of the levels of the SCLC stem cell markers CD133 and ABCG2. SCLC H446 tumor-bearing mice after treatment via Cc@CLNs showed a lower tumor size and weight [66].

Besides, the properties of lipid NCs also make them suitable for gene delivery, so in 2019 a study was performed on MiR-660 upregulating. MiR-660 has known as a tumor suppressor miRNA in lung cancer cells and also can block the migration and invasion of tumor cells. P53 as a tumor suppressor gene regulate by mouse double minute 2 (MDM2) and inhibition of MDM2 play an important role in suppression of tumor

growth both in vitro and in vivo (patient-derived xenograft (PDX) models of lung cancer). In this study Coated Cationic Lipid-nanoparticles (CCL) were used to deliver miRNA-660 (CCL660). Results demonstrated by overexpression of miRNA-660 tumor growth decreased, and by a reduction in MDM2, anti-cancer activity of P53 was confirmed and expression of miR-660 blocked H460 metastatic lung cancer cells [67].

3.1.2 Polymeric nanocarriers (PNCs)

Biodegradable polymers such as poly(lactic acid) (PLA), poly(lactic-co-glycolic) acid (PLGA), gelatin, albumin, chitosan, polycaprolactone, and poly-alkyl-cyano-acrylates are the most popular inexpensive polymers that are used in synthesizes of NCs. [68]. These solid structures released drugs in response to pH, light and redox potential [69].

Production of PNCs in detail brought in previous references that those who are interested to know more can refer to them. There are various PNCs that we mentioned some of them in the following, they have covalent and non-covalent interaction with specific proteins to improve and compensate for PNCs problems such as poor solubility and poor bioavailability [70]. Investigation of studies in the last 2 years demonstrates that these NCs play a significant role in the treatment of lung cancer. In vitro and in vivo studies demonstrated PNCs are without any problem (e.g., toxicity) to cells and host. Results of gathered studies indicated PNCs are more common and effective in comparison with lipid-based NCs. Due to their high diversity, different ranges of drugs and agents are connected to them to deliver to lung cells of tumors. In vitro experiments in PNCs showed high internalization and cytotoxicity and disrupt some crucial cancer signaling. Moreover, as mentioned in the Lipid-based NCs section in vivo experiments in PNCs indicated a reduction in tumor growth and volume and more drug dispersion in lung tumors.

In 2019, Quercetin (QR) loaded on T7 surface-functionalized PEGylated liposomes that contained soy-phosphatidylcholine (SPC) was used for an experiment on A549, MRC-5 cells and A549-Luc orthotopic lung tumor-bearing BALB/c nude mice. Increasing cytotoxicity, cellular uptake and rate of penetration in 3D lung tumor spheroids and induction of apoptotic effect and inhibition of tumor growth were the results of this study [71].

In another research, polypyrrole (Ppy)–polyethylenimine (PEI) nanocomplex (NC) was evaluated for the delivery system. One of the problems of Ppy for synthesizing of NC was its poor insolubility in water. For solving this problem some agents such as heparin, polyvinyl acetate, and chitosan were used for coating this polymer and increased their stability. Negatively charged lung cancer cells absorbed cationic Ppy–PEI NC and leading to less damage to surrounding cationic inflammatory tissue. Mitochondria dysfunction and ROS (Ppy–PEI NC could produce few ROS and hydrogen peroxide) are two important factors that causing cell apoptotic process [72].

Gong et al. used a pH-responsive methoxyl poly(ethylene glycol)-poly (aspartyl(dibutylethylenediamine)-co-phenylalanine) (mPEG-P(Asp(DBA)-co-Phe)) for delivery of afatinib as inhibition of epidermal growth factor (EGFR) and doxorubicin as a DNA-damaging chemotherapeutic to A549 lung cancer cells. Results showed by pH reduction, the release of both of them increased also they could cytotoxicity and apoptotic in cancer cells, and in vivo experiments indicated tumor growth and volume decreased in treatment mice [73].

Biodegradable PLGA NCs are another PNC that encapsulates the erlotinib cyclodextrin (Erlo-CD) complex. Enhanced cellular uptake caused higher cytotoxicity.

This NC leads to erlotinib resistant A549 cells became sensitive to erlotinib and tumor growth and metastasis decreased. Evaluating caspase-3 and caspase-7 activity showed inducing apoptosis in A549 cells, and 3D-spheroid cell culture was utilized for better mimics the physiological solid tumor [74].

On the other hand, various PNCs recently were evaluated. Alectinib as a clinical drug with adverse side effects used for target therapy in ALK-positive NSCL with dual-targeted (magnetic/TAT) NCs that made by poly (ethylene glycol) (PEG) and poly (hexyl ethylene phosphate) (PHEP). Magnetic targeting causing the exit of alectinib from vessels into tumor tissue and TAT targeting enhances tumor cellular uptake [75].

Moreover, in a recent study PNCs (PLGA) encapsulate sorafenib (SF) used for the treatment of NSCLC. Sorafenib is an inhibitor of Ras/Raf/MEK/ERK and has an anti-tumor activity via downregulation of the VEGFR-2/platelet-derived growth factor receptor (PDGFR)-β. Tumor accumulation, cytotoxicity and local release are other properties of SF NP [76].

S-HAp nanospheres with PEG and folic acid (FA) is another pH-responsive NC that delivers DOX to tumor tissues [77].

pH and redox-sensitive NPs is another PNC made from PEG-SS-PBAE-PLGA (PSPP) to encapsulate the platinum complexes of curcumin (Pt-Cc@PSPPN). Pt-Cc@PSPPN showed excellent stability. In A549 cells, cytotoxicity and apoptotic effect increased due to higher cellular uptake, and in vivo experiments, on A549 xenograft tumor-bearing nude mice indicated local bio distribution and antitumor activity of Pt-Cc@PSPPN. For anti-metastasis effect, CD31, VEGF, and MMP2 antibodies were evaluated and indicated metastasis inhibition [78].

Also in 2020, PEG-PLGA NPs enclosed febuxostat (FBX) (FBX–PLGA–PEG). The viability of A549 cells decreased. Evaluating of caspase 3 activity showed treatment by FBX–PLGA–PEG induced cellular apoptotic and cell cycle arrest [79].

In other investigations, Vaidya and colleagues indicated a kind of NPs made from PEI as a cationic stabilizer and coating bovine serum albumin (BSA) for a reduction in toxicity, controlled quinacrine (QA) release and accumulation of particles in the target region. Higher cellular uptake, cellular cytotoxicity, apoptosis and cell cycle arrest achieved in A549 cells. These results were obtained by evaluating p53, p21, LC3B, p62 and cleaved caspase-3. To better predict the physiological interaction in cytotoxicity and cell viability, the 3D-spheroid cell culture study was performed [80].

Another property of polymers, PEG–PLA and Pluronic P105 could encapsulate PTX (PEG–PLA/P105/PTX micelles). PEG–PLA/P105/PTX micelles combined with ambroxol (Ax) causing toxicity in A549 cells. PEG–PLA/P105/PTX micelles in combination with Ax lead to anticancer effect and excellent biodistribution [81].

Interestingly, PNCs have also been reported to be able to gen delivery, for example in 2019 siVEGF and chemotherapeutics etoposide (ETO) encapsulated by PEGylated histidine-grafted chitosan-lipoic acid (PHCL). Internalization in A549 cells treated by PHCL-Lip/ETO-siVEGF augmented, and by downregulation of VEGF via siVEGF cellular uptake enhanced and proliferation and metastasis decreased. For assessment of the ability of NPs in penetrating, A549 tumor spheroids were constructed (**Figure 6**) [82].

In another experiment, Cyanine 3 (Cy3)-labeled siRNA conjugated to HA-modified chitosan NPs (sCS NPs-HA) was prepared to use for experiment on A549 cells and xenograft tumor model female BALB/c mice. Cy3-labeled siRNA specifically delivered to A549 cells due to the CD44 receptor by sCS NPs-HA, and caused inhibition in cell proliferation by downregulation in BCL2. In vivo experiments showed tumor size and growth reduction [83].

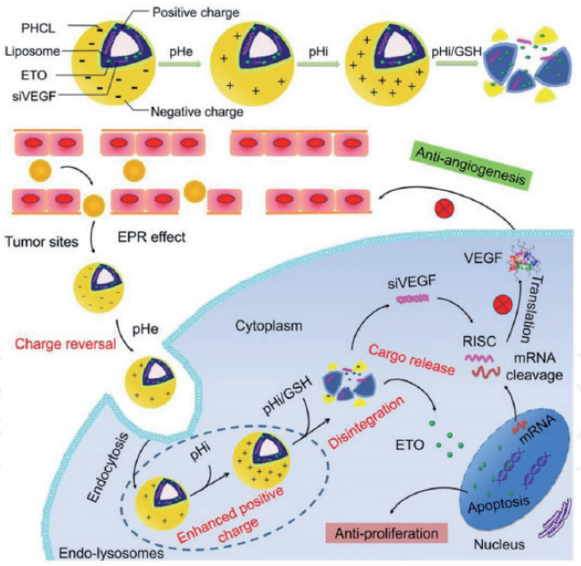

Figure 6.
VEGF siRNA and etoposide delivery via multi-functional nanoparticles for non-small cell lung cancer treatment. This figure was obtained with permission from [82] under the terms of creative commons CC BY license.

3.2 Inorganic nanocarriers

3.2.1 Quantum dots

Quantum Dots (QDs) by nanocrystal structure are semiconductors that gave them the ability to emit fluorescence from visible to infrared wavelengths. Surface modification of QDs gave them the potential in cancer imaging which is essential for choosing the appropriate cancer therapy [84]. Among the features of QDs are the following: do not react with drugs, have a high capacity for drugs encapsulated, low toxicity, good biocompatibility, strength and stability. In addition to the properties mentioned, their very small size (2–10 nm in diameter) makes them very efficient in drug delivery for lung cancer therapy [85].

One of the cases of QD-NCs as a system delivery is a ZnO QDs-based pH-responsive which coated by dicarboxyl-terminated PEG to increase the stability was prepared. CD44 as a marker in A549 cancer cells bind to HA that exist in ZnO QDs, and DOX by covalent interaction was loaded on ZnO QDs. In acidic endosome/lysosome, Zn^{2+} in ZnO QDs controlled the release of DOX that both of them used for lung cancer therapy via antitumor effect [86].

DOX and Cyclosporin (CsA) loaded on photoluminescent Graphene QDs encapsulated mesoporous NPs (GND@MSNs). Cell cytotoxicity was evaluated in A549 and HEL-299 Cells. GND@MSNs+DOX + CsA by inducing DNA damage causing apoptosis and cell cycle arrest [87].

3.2.2 Mesoporous silica nanocarriers (MSNCs)

MSNCs can be loading a variety of drugs and agents. The size of these carriers is crucial for effective drug delivery. The pore size in MSNs can be different, and internalization and biodistribution are related to the shape of them [88]. For instance, DOX deliver by an NC system made from d-a-tocopheryl polyethylene glycol 1000 succinate (TPGS)-functionalized polydopamine-coated MSNCs (MSNs-DOX@PDA-TPGS). This system released drugs in response to a decrease in pH. Both the A549 cells and drug-resistant A549 cells were tested for evaluating cytotoxicity and cellular uptake. Charge of the tumor cell membrane is negative

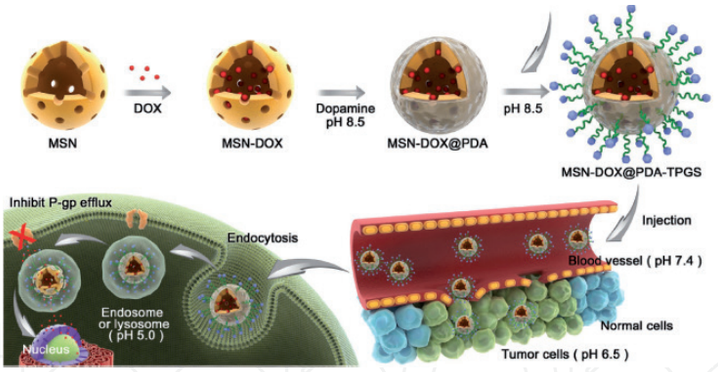

Figure 7.
TPGS-functionalized mesoporous silica nanocarrier for DOX delivery against lung cancer cells. This figure was obtained with permission from [89] under the terms of creative commons CC BY license.

and these NPs because free amines and ammonium groups of TPGSNH2 are slightly positive that enhance cellular uptake. The existence of TPGS is a factor for reducing drug resistance. Histological analysis showed the antitumor activity of MSNs-DOX@PDA-TPGS (**Figure 7**) [89].

4. Gas plasma in conjunction with nanoparticle for lung cancer treatment

Advances in digital technologies have created new opportunities for diagnosing, managing and treating disease. Several examples of advanced nanotechnology and digital technology have already been approved for the diagnosis and treatment of diseases. Plasma therapy, which has emerged as new healthcare technology, shows great potential for treating many diseases, including cancers with few or even no side effects [90].

In addition to the need to develop new healthcare methods, it is crucial to improve the efficacy of existing clinical used strategies such as chemotherapy drugs. The reality is that we need a solution to sustainable development in oncotherapies. This can only be achieved by combining existing and future methods. Plasma technology alone or in conjunction with nanomaterials shows high potential benefits along with chemotherapeutic strategies, minimizes side effects and increases the selectivity performance. On the other hand, the combination of plasma and nanotechnology leads to a multidisciplinary healthcare package that significantly improves the treatment outcomes of the disease and reduces the economic burden for healthcare in the community, as well as many solves problems related to the health care system (**Figure 8**) [10, 14, 17, 91].

Gas plasma and nanotechnology are the basis for the launch of future oncotherapetics agents. Synergistic effects of CAP, PAM and NCs with conventional therapy like chemotherapy, radiation therapy, pulsed electric fields, and plant origin have been discussed in recent years to improve the effectiveness of these methods. CAP and NPs and are fabricated independently and often along different ways to meet a range of biomedical challenges.

There are interesting similarities in their interaction with living cells and tissues, and these are directly related to the characteristics and scope of their therapeutic solutions, especially chemical reactivity, selective action against pathogens and cancer cells, immunity to healthy cells and tissues, and transmission. Targeted drugs are reflected by them into diseased tissues. It is time to consider synergies and the simultaneous combination of plasma-nanoparticles and their associated

benefits for the development of effective therapies improved selective effects and high safety for modern oncology. In this section of the chapter, we focus on the created opportunities for linking plasma technologies and nanocarriers in lung cancer treatment [8–12].

There is only two work about the application of gas plasma and nanoparticle combination in lung cancer oncotherapy. Yu et al. first explored the targeted delivery of a PTX loaded PLGA-based delivery system by magnetic iron oxide nanoparticles (MNPs) in conjunction with plasma treatment. After encapsulating PTX within nanoparticle release of PTX to tumor significantly was modified.

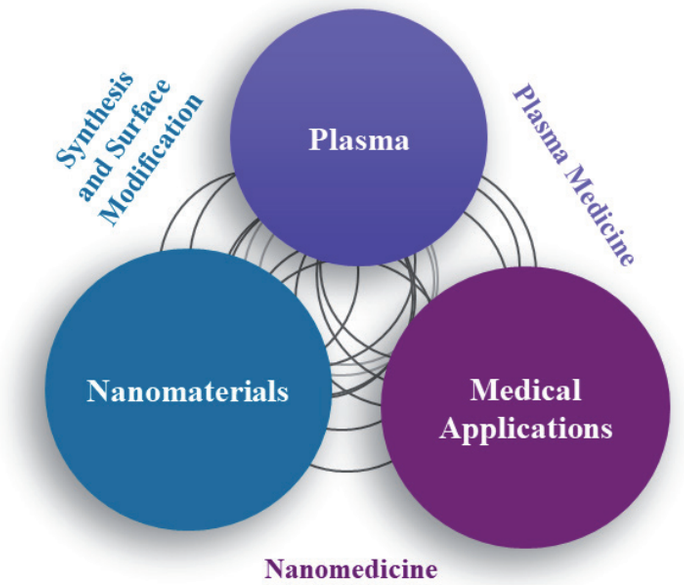

Figure 8.
Gas plasma, nanomaterials and their interaction alongside the medical applications of these two technologies.

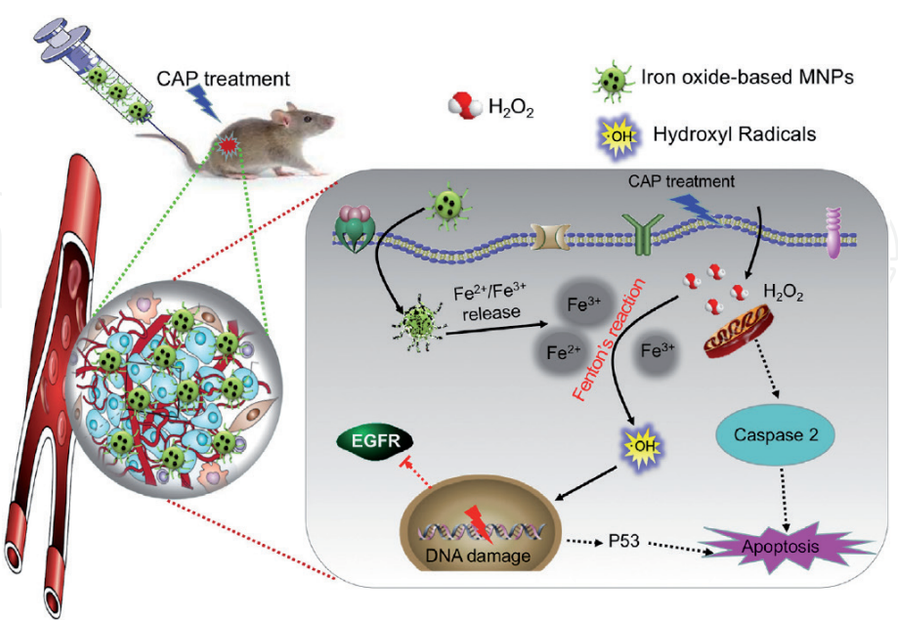

Figure 9.
Molecular mechanisms of MNPs enhancing tumor-selective killing effect of CAP. CAP-originated reactive species will cause a noticeable rise of intracellular H_2O_2, Fe^{2+}/Fe^{3+} released from the lysosome containing MNPs could catalyze H_2O_2 into OH., which cause the injury of cancer cells, such as inducing mitochondria-mediated apoptosis and double strand DNA breaks. This figure was obtained with permission from [92] under the terms of creative commons CC BY license.

Cytotoxic effects of various combinations of the gas plasma, PTX, PTX-loaded electrosprayed nanoparticles, and nanoparticle/plasma evaluated in the multimodal treatment of lung cancer cells. The data verify that plasma increased production of ROS enhanced the efficacy of nanoparticle, and induce apoptosis in A549 cancer cells [42].

Recently this group shines new light on these debates through an examination of lung cancer treatment's underlying mechanism. This study set out to compare and gain further understanding of the mechanism of the gas plasma alone and in combination with iron oxide-based MNPs treatment modalities. The simultaneous combination of gas plasma and MNPs is more promising in inhibiting the proliferation and induction of apoptosis. Plasma via depressing pERK and pAKT inhibited lung cancer cells but synergizing of two modalities induced EGFR downregulation. These results were also confirmed by inhibition of tumor xenograft growth. Finally, plasma and MNPs are highly promising combination treatments for aggressive forms of lung cancer (**Figure 9**) [92].

5. Conclusion and perspective

Cancer is increasingly becoming a chronic disease and has the lower success of a clinical trial among other diseases. As the current trend continues, lung cancer will remain a major challenge to healthcare systems. Therefore, investing in new technologies is essential to overcome this challenge. Many of the previous works about plasma oncotherapy for lung cancer have been performed at the in-vitro level. Therefore, there is still a long way to go before studies close to clinical applications, but in the short term, due to the achieved promising results, multimodal nature of plasma, the ability to synergistically with conventional drugs, it has given us great hope.

Nanocarriers for drug delivery system seems to be a reliable strategy for the biopharmaceutical industry. They have many advantages over conventional therapies and they have a bright future due to their inherent properties. The recent advances achieve in experimental researches such as in vitro (2D/3D cell culture), in vivo and ex vivo of tumor-target nanocarriers make it possible for use of this strategy for clinical trials for use as monotherapies or in combination with chemotherapeutics and it is necessary to standardize this new therapy, till could be approved and suitable for use in humans. This requires that research move from formulation-based approach and laboratory work towards patient-centered experiments.

Advances in nanotechnology and gas plasma have given us hope for cancer treatment. These technologies target the tumor selectively and the combination of gas plasma and nanotechnology have the potential to revolutionize cancer therapy. The integration of plasma science, chemistry, engineering, and oncology proved to be a powerful approach to cancer research, leading to technological and medical breakthroughs. To fully realize the promise of plasma and nanotechnologies in oncology, funding from government agencies and International Research Centers should be specifically targeted towards research at the intersection of these disciplines. Indeed, Investments have been made in this area in recent years, but it not enough due to the high potential of these two technologies.

Given current problems with various non-standard devices and nanoparticles, current investments should be targeted at the first step in developing standardization of plasma devices and nanoparticles. The second phase is the commercialization of nano and plasma technology.

Conflict of interest

The authors have no conflict of interest to declare.

Acronyms and Abbreviations

CAP	Cold Atmospheric pressure Plasma
PAL	Plasma Activated Liquid
RONS	Reactive Oxygen-Nitrogen Species
NSCLC	Non-Small Lung Cells
ADC	Adenocarcinoma
SCC	Squamous Cell Carcinoma
PAM	Plasma-Activated Medium
NCs	Nanocarriers
HOCl	Hypochlorous acid
H_2O_2	Hydrogen peroxide
NHBE	normal human bronchial epithelial
MAPK	mitogen-activated protein kinase
CAFs	Cancer-Associated Fibroblasts
LbL	Layer-By-Layer
NPs	Nanoparticles
LF	Lactoferrin
HA	Hyaluronic Acid
BER	Berberine
RAP	Rapamycin
SLS	Sodium Lauryl Sulfate
HIP	hydrophobic ion pair
PBS	Phosphate Buffered Saline
VEGF	Vascular Endothelial Growth Factor
Nrf2	Nuclear Factor E2–Related Factor 2
NLCs	Nanostructured Lipid Carriers
APG	Apigenin
DTX	Docetaxel
CET	Cetuximab
PTX	Paclitaxel
DMN	5-Demethylnobiletin
LPNs	Lipid Polymeric Nanoparticles
CDDP	Cisplatin
Afa	Afatinib
SCLC	Small-Cell Lung Cancer
Cc	Curcumin
MDM2	Mouse Double Minute 2
CCL	Coated Cationic Lipid-nanoparticles
PLA	Poly Lactic Acid
PLGA	Poly Lactic-co-Glycolic Acid
SPC	Soy-Phosphatidylcholine
Ppy	Polypyrrole
(mPEG-P(Asp(DBA)-co-Phe))	Methoxyl Poly Ethylene Glycol-Poly Aspartyl Dibutylethylenediamine-Co-Phenylalanine
EGFR	Epidermal Growth Factor
Erlo-CD	Erlotinib Cyclodextrin

APT	Aptamer
PEG	Poly Ethylene Glycol
PHEP	Poly Hexyl Ethylene Phosphate
SF	Sorafenib
PDGFR	Platelet-Derived Growth Factor Receptor
FA	Folic Acid
FBX	Febuxostat
PEI	Polyethyleneimine
BSA	Bovine Serum Albumin
QA	Quinacrine
ETO	Etoposide
PHCL	PEGylated Histidine-grafted Chitosan-Lipoic acid
QDs	Quantum Dots
CsA	Cyclosporin
MSNCs	Mesoporous Silica Nanocarriers
TPGS	Tocopheryl Polyethylene Glycol 1000 Succinate
MNPs	Magnetic Iron Oxide Nanoparticles

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