Chapter

Nano Technology and Gas Plasma as Novel Therapeutic Strategies for Ovarian Cancer Oncotherapy

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Abstract

Ovarian cancer (OC) is associated with a high rate of resistance to most chemotherapy drugs and thus novel therapies are crucial to overcoming these obstacles. The technological advances in nanotechnology make it possible to adapt these approaches for the treatment of chemo-resistant OC. In parallel, it is also evident that this emerging technology plays crucial roles in other medical areas including wound healing, treatment of viral infection and applications in dentistry. With the advancement of nanotechnology, nano dependent therapies are attractive viable alternatives to conventional therapies for various diseases, especially cancers. Nanoparticles (NPs) are a suitable platform for cytotoxic agent delivery and aiding early diagnosis of disease, which can lead to improving outcomes for these patients. Gas plasma oncotherapy is an innovative modality and shows huge potentials in cancer treatment and may emerge as the fifth cancer treatment modality together with surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy. The combination of nanoparticle and gas plasma therapy could lead to the discovery of an alternative effective treatment approach in these resistant tumors leading to improvement of OC prognosis. Here, we highlighted the two novel modalities with known multiple biological targets and underlying mechanisms appropriate for their application in OC treatment. This chapter explores the utility of combination or multimodal of novel nanotherapeutic agents in the treatment of OC.

Keywords: ovarian cancer (OC), gas plasma, nanoparticles, chemoresistance, reactive oxygen and nitrogen species (RONS), physical effects (UV, EM)

1. Introduction

Emerging clinical evidence indicates OC is a disease associated with poor survival and high mortality and the current situation of OC oncotherapy has created a major problem for the health system [1, 2]. Due to the limited therapeutic results of conventional modalities, the majority of efforts in OC treatment studies focus on new therapeutic strategy achievement. The new perspectives for OC management should not have been unwanted side effects such as drug resistance and toxicity [3, 4]. Nanotechnology and gas plasma offering a promising alternative to conventional OC therapies [5–7].

Nanotechnology uses nanomaterial for a wide range of various purposes including biomedicine, energy, electronics, environment, food, and textile. Nanoparticles (NPs) have been engineered from various materials with unique properties as drug

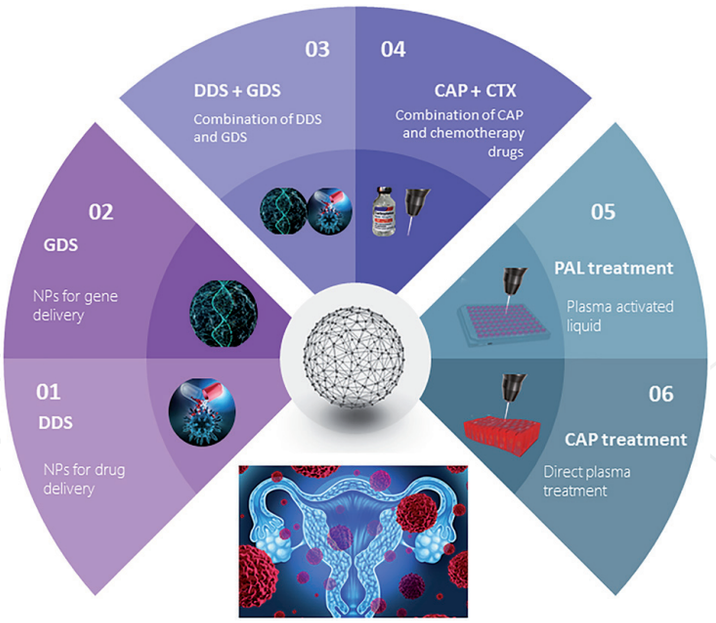

Figure 1.
Schematic illustrating of all reviewed treatment modalities for OC oncotherapy. DDS (drug delivery system), GDS (gene delivery system), CAP (cold atmospheric plasma), PAL (plasma activated liquid), CTX (chemotherapy).

vehicles to treat a peculiar disease [8–10]. Cancer nanomedicine creates a suitable strategy for modern oncotherapy and has attracted a lot of attention in recent years. The therapeutic nature of nanoparticles, drug delivery, and gene delivery are important foundations for increased attention to this new field [10–12].

The gas plasma that generates through conducting noble gas to the paired electrode at room temperature offers a new category of oncotherapy strategy in a short time [13]. Gas plasma oncotherapy will become an option for cancer treatment shortly, given its fast-development and multifunctional nature. This technology has provided the link between multidisciplinary scientific areas including physics, chemistry, biology, and medicine to address problems and offers an effective route for various oncotherapy challenges [14–16]. Multiple physical and chemical agents including charged particles, electric fields, ultraviolet (UV) radiation, and reactive oxygen and nitrogen species (RONS) involved in the efficacy of gas plasma [15].

NPs and gas plasma have risen as a promising therapeutic option for the treatment of ovarian malignant. These technologies exhibit comparable selectivity against tumor cells and provide a more efficacious and safe option for OC oncotherapy. The literature has been shown that NPs and gas plasma remarkably enhance the delivery of anticancer drugs and improve the efficacy of treatment and minimize the adverse effects of chemotherapeutic agents in healthy cells [16, 17].

This chapter presents the antitumor effect of gas plasma in combination with nanoparticle-based technology, as a new and most promising multimodal cancer therapy (**Figure 1**). Here, we provide a comprehensive and prospective review of the application of novel plasma and nanotechnology for the combination or multimodal OC oncotherapy.

2. Ovarian cancer: conventional treatment and resistance to chemotherapy

OC is one of the most common gynecological malignancies throughout the world and the fifth leading cause of cancer-related deaths among women in the

United States [18]. According to the American Cancer Society statistics, it was estimated that there would be 22,530 women who will receive a new diagnosis of OC and about 13,980 women will die from the disease in 2019. Carboplatin and platinum-based chemotherapy were used as the first choice to treat this type of cancer. Findings indicate who patients respond well to the initial treatment regime acquired drug resistance of the tumor after a time duration [19].

The main mechanisms of carboplatin resistance include reducing drug accumulation by altering the uptake/flow index, inactivating cisplatin by increasing the level of intracellular thiols such as glutathione, metallothionein, or other sulfur-containing molecules, increasing the repair capacity of platinum-induced DNA damage at the total level. The genome and DNA sequence become specific and the failure of the apoptotic response. Increasing the delivery of platinum to the tumor, a combination of platinum drugs with targeted molecular agents, modulators of platinum resistance, and new platinum drugs that target resistance mechanisms are the most important strategies being pursued that after intensive studies by many researchers are working to circumvent the resistance of cisplatin and carboplatin [20, 21].

Mortality trends in OC show the inefficiency of current therapeutics modalities except for PARPi and anti-VEGF. Thus, it is urgent to explore novel and efficient therapeutic options for epithelial OC that have the most lethal world gynecologic malignancy.

3. Nanotechnology as a therapeutic option for ovarian cancer

3.1 Nanoparticles

Nanotechnology as a science for minimizing material with particular properties has been used in various fields and multidisciplinary sciences such as chemistry, biology and physic. NPs in medicine application is called nanomedicine and it is utilized for the profit of human health and well being. In the field of nanomedicine, NPs in diagnosis, pharmacological treatment at a molecular level, molecular imaging, tissue engineering and regenerative medicine are widely used [9, 12, 22].

Agents through surface interaction, encapsulation, or entrapping loaded into NPs, and based on their properties avail for active and passive drug delivery. NPs based on their diverse structure like branched, spherical, or shell shape offer to become suitable for drug delivery to specific diseases such as cancer. Conventional chemotherapy distributes in the whole body and destroys both normal and tumor cells, as well as, after a while cancer cells become resistant to drugs [11, 23].

Controlling drug delivery and accumulation in tumor cells caused to require lower drug concentration for improving oncotherapy and diminishing the side effect for normal cells. Released agents from NPs are controlled by external or internal stimuli like pH, electric or magnetic field, temperature, redox and sound, and it ameliorates target therapy [24].

The optimal nano-size range for increase efficiency is typically 1-100 nm. There are different types of NPs for instance polymeric NPs, quantum dots, lipid-based NPs, mesoporous silica and dendrimers. Biodistribution, circulation time, stability, bioavailability, size, shape and surface charge are common characteristics of NPs that play an important role in their functioning [25].

For experimental and clinical trials, preparing an NP requires attention to some properties for better quality. Cellular recognition by specific antibodies is necessary for target delivery to specific cells [26]. NPs shouldn't stimulate the immune system to prevent degradation of them and their agents [27].

In gen delivery NPs carrying nucleic acids containing microRNA (miRNA), short hairpin RNA (shRNA), antisense oligonucleotides (AONS) and small interfering RNA (siRNA), with the silencing or downregulation purpose of genes or proteins which related to drug-resistant, angiogenesis or metastasis are used for improving oncotherapy and resolve the conventional therapy limitation [28]. We summarize nanotechnology based therapeutics in **Figure 2**. Here, we review the pre-clinical application of NPs for OC oncotherapy.

3.2 Drug delivery

In this section, we gathered some experiments that used different types of NPs for drug delivery to overcome the common problem in the treatment of OC as a lethal gynecological cancer worldwide, which almost diagnosis in late stages with the high rate of drug resistance for diagnosis and treatment. The advantages encourage researchers to utilized NPs consist of: NPs are used for drug delivery that lead to more effective in OC treatment. Also, reduce side effects due to specificity targeted NPs to OC cells.

SKOV3 and A2780 are the most usable cells for in vitro experiments that are treated by different kinds of drug loaded NPs. NPs are modified by several ligands such as hyaluronic acid, folic acid and HER2-targeted ligand for enhancing target delivery. GSH (Glutathione)-sensitive and pH-sensitive are other properties of these NPs that improve their effectiveness. As results showed the stability and biodistribution of these NPs that encapsulate drugs are very impressive. Increasing cellular uptake and cytotoxicity by inducing apoptosis or necrosis for in vitro experiments, and tumor growth and volume inhibition in the level of in vivo are the usual results that have been obtained.

The most barrier to entrance NPs into the cells through endosomes is an endosomal escape. Transferrin (Tf) and octaarginine (R8) play role in endosomal scape and specific delivery respectively. IAR-CPP R8 and Tf linked to the surface of PEGylated liposomes, which encapsulated doxorubicin (DOX) (DOXIL®) for

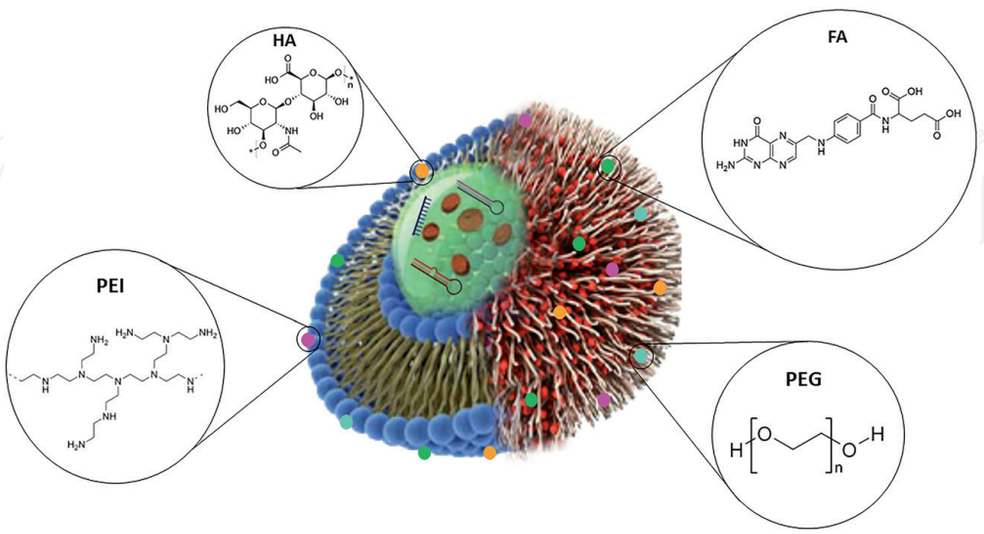

Figure 2.
Drugs or RNA interference (miRNA/siRNA/shRNA) loaded to lipid-based or polymeric nanoparticle as common nanocarriers are designed for delivery to OC cells in order to oncotherapy. Surface of these nanoparticles modified by different ligands such as hyaluronic acid (HA), folic acid (FA), Polyethylene glycol (PEG) and Polyethylenimine (PEI) for enhancing efficiency.

specific target therapy in A2780 cells. Results indicated efficiency in both entry pathways and accumulation in tumor cells increased [29].

3.2.1 Modified NPs: HA, FA, HER2 antibody for specific targeting

Adding a ligand to the surface of NPs enhances drug delivery effectiveness to OC cells. Hyaluronic acid (HA) that is linked to CD44 which is a cell-surface glycoprotein and expresses specifically in tumor cells improves target delivery [30]. In the following, we mention an example that NPs modified by HA. Cisplatin-loaded polyarginine-HA NPs (CIS-pARG-HA NPs) were produced in this study, to overcome peritoneal carcinomatosis which generally diagnosis in the late stage of OC patients. In vitro studies on SKOV-3 cells showed reduced cell viability, by cooperation CD44 in cancer cells and an increase in cellular uptake. Also, the effectiveness of CIS-pARG-HA NPs improved, when these NPs were administered by pressurized intraperitoneal aerosol chemotherapy (PIPAC) due to the penetration into the peritoneal tumor [31].

Folate receptor α (FRα) is another marker that overexpresses in OC cells, so modifying NPs surface by folic acid (FA) is another mechanism in specific target delivery. Using FA due to low immunogenic, inexpensive and stable properties, is more welcomed. Below we gather two examples in the level of in vitro and in vivo, to evaluating target delivery by FA ligand which binds to NPs [30].

PTX loaded PLGA NPs modified by FA for oncotherapy. For comparison, modified NPs with non-modified NPs, were used to treat SKOV3 cells. FA improved the effect of NPs and rise up the cytotoxicity by increasing cellular uptake, and disrupt in cell division and apoptosis process [32]. In another study, Nanoemulsion (NE) as a delivery system was used to loaded docetaxel (DTX) and FA for treating OC. Cell treatment by this nanocarrier enhanced cytotoxicity due to the DTX, while treatment transgenic mouse model of ovarian carcinoma induced inhibition in tumor growth and volume [33].

The overexpression of the HER2 receptor is another specific marker that contributes to OC. CIS and trastuzumab and HER2-targeted antibody conjugated with poly(lactic-co-glycolic) NPs target HER2 receptor. CIS via impressing on DNA conformational and by a dose-dependent manner cause cytotoxicity and apoptosis in SKOV3 cells. The effectiveness of this delivery system after modifying by trastuzumab and chitosan increased in both in vitro and in vivo experiments [34]. Cell viability in HER-2-overexpressing cell line can also decrement by treating them with poly(butylene adipate-co-butylene terephthalate) (Ecoflex®) NPs by adding an aptamer engineer to improving the efficacy and reducing the side effects of DTX. For evaluating antitumor activity and biodistribution, tumor-bearing B6 athymic mice received NPs intravenously and significant results were obtained [35].

3.2.2 Control drug released from NPs: pH and GSH sensitive NPs

pH-sensitive NPs are widely utilized for drug delivery. Drugs released from NPs are controlled by various factors like pH. A2780 as a CIS sensitive and A2780DDP as a CIS resistant OC cells treated by pH-sensitive Fe_3O_4 NPs encapsulating CIS for reducing its side effect and drug resistance. NPs@CIS cause more internalization and in the following more drug accumulation in OC cells. In both cell lines, cytotoxicity and apoptosis increased because of the drug entry into the cell nucleus. The existence of an external magnetic field for in vivo experiments enhanced the antitumor efficacy and inhibition toxicity in normal tissues [36].

In another study, Tariquidar (TQR) and DOX loaded a pH-sensitive liposome formulation (pHSL) (pHSL/TQR/DOX) was prepared to overcome multidrug

resistance. pHSL made from CHEMS (cholesteryl hemisuccinate), DOPE (1,2-dioleoyl-sn-glycero-3-phosphoethanolamine) and PEGylated lipid which DOX and TQR placed in the water and lipid phases respectively and this nano vehicle prolong circulation. Cytotoxicity was investigated by treatment OVCAR8/ADR cells with pHSL/TQR/DOX (**Figure 3**) [37].

Combination of FA ligand for specific target delivery and pH-sensitive NPs proposed phenomenal nanocarrier for ovarian oncotherapy. Magnetic NPs (MNPs) and MTX through carboxylic acid groups and amino groups of chitosan linked to chitosan copolymer and prepared thermos and pH-sensitive MTX-CSC@MNPs that conjugate with erlotinib (ETB) for target delivery. Since MTX and FA are similar structurally this nano vehicle absorbed with folate receptor on OVCAR-3 cells and prompt cytotoxicity and apoptosis induced by ETB [38]. Moreover, pH-sensitive Glucose/gluconic acid-coated magnetic NPs that linked to FA in the surface, enclosed DOX. External magnetic fields improve drug release in tumor tissue. For evaluating cell viability A2780, OVCAR3 and SKOV3 cells treated by these NPs and results demonstrated an increase in internalization and cytotoxicity. Analyzing the tissues of the SKOV3-Luc cell-xenografted nude mouse model showed accumulation of the drug in tumor cells more than other parts of the body that it causes to block the tumor growth [39].

Drug released is also controlled by intracellular GSH concentration. GSH sensitive polymersomal DOX nano vehicle that modified by GE11 peptide (GE11-PS-Dox) is one of these NPs produced for treatment SKOV3 cells with a high level of epidermal growth factor receptor (EGFR). After drug delivery to tumor tissue and cancer cells, DOX enters the cell nucleus and inhibits tumor progress and increases cytotoxicity. The efficiency of this treatment is more than Lipo-Dox or Dox alone (**Figure 4**) [40].

3.2.3 Novel approaches drug delivery platform with the integration of different factors

In some cases, to ameliorate the level of treatment dual drug delivery suggests. For example, for carrying quercetin and gefitinib individually and together to PA-1 OC cells polyvinylpyrrolidone (PVP)-functionalized graphene oxide NPs (GO-PVP-NPs) as a system delivery was used. The results indicated combination delivery is more effective than individually in PA-1 cells [41].

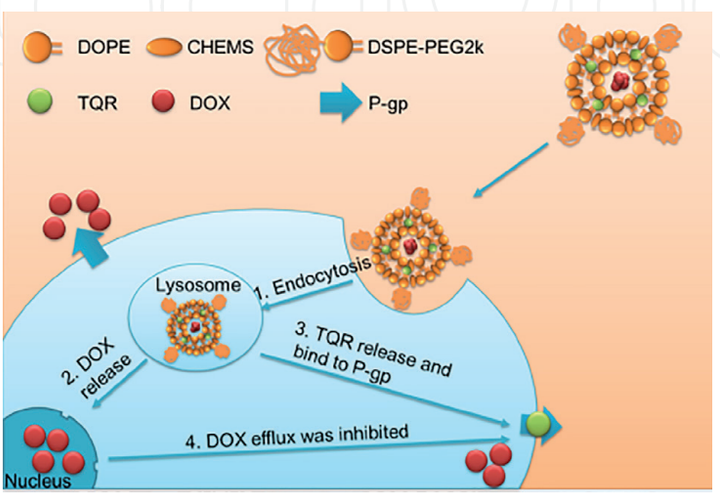

Figure 3.
Tariquidar and doxorubicin conjugated with pH sensitive liposomes to overcome multidrug resistance of OC cells. This figure was obtained with permission from [37] under the terms of creative commons CC BY license.

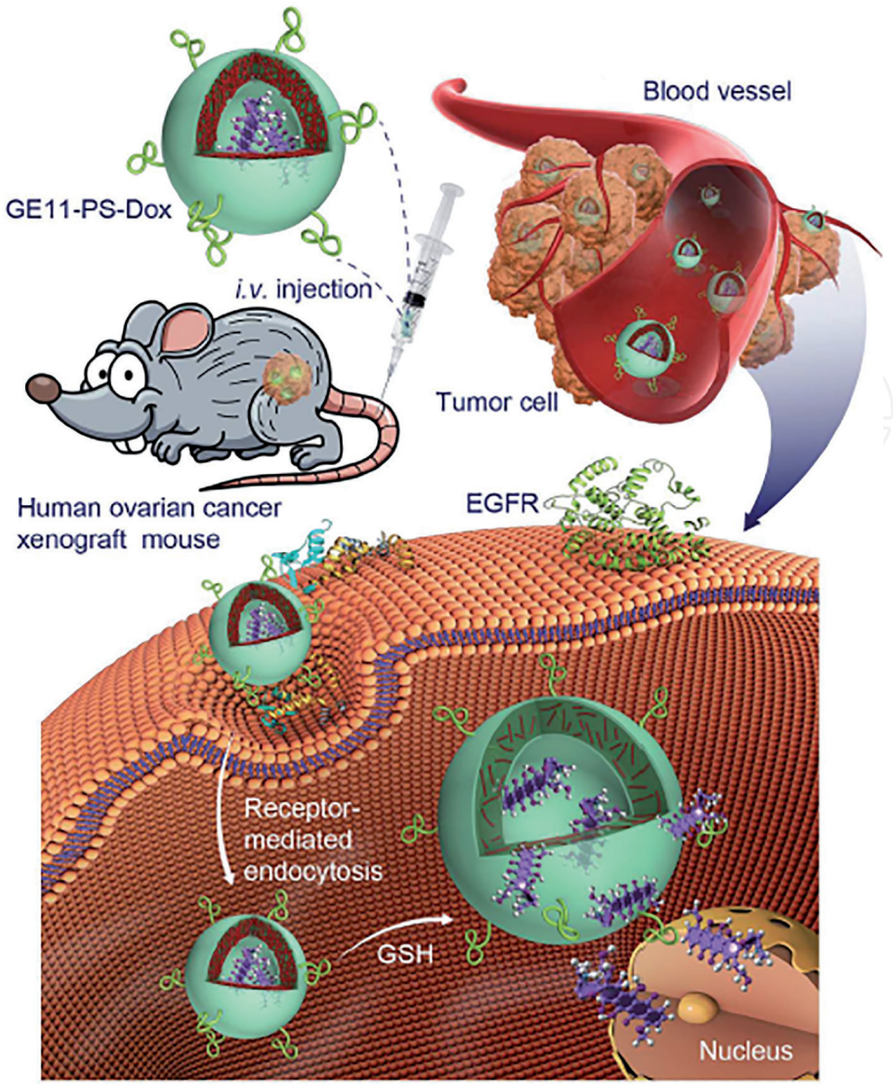

Figure 4.
Polymersomal doxorubicin with GE11peptide designed as an alternative to Clinical Liposomal Formulation for ovarian oncotherapy. This figure was obtained with permission from [40] under the terms of creative commons CC BY license.

Polymeric NPs and lipid-based NPs are the most usable nanocarriers that sometimes a combination of them make NPs suitable for drug delivery with high efficacy. In this experiment, a Pluronic F127 and a lipid-PEG stabilizer were used to generate NPs which have internal cubic phases are called cubosomes (CB) and external sponge phase. These NPs are conjugated with PTX against HEY cells and disrupt EGFR that overexpress in OC. Decreasing the cell viability and inhibiting the tumor growth are the results of this study [42].

Platinum-resistant OC (PROC) isn't possible to treat by conventional therapy for solving this problem, PROC is treated by CIS and wortmannin (Wtmn) as a DNA repair inhibitor conjugated with PEG-PLGA NPs. After treated A2780 cells, γH2AX foci as a DNA double-strand breaks marker analyzed for Wtmn activity and cytotoxicity. High solubility and stability are other properties of this dual nanocarrier. In vivo studies displayed the low concentration of drugs could inhibit tumor growth [43].

Nucleic acid-based NPs is another nanovehicle for transferring drugs to OC cells. For instance, an annexin A2 aptamer (ndo28) bind to pRNA-3WJ NPs and design a GC rich sequence in NPs for linking DOX. Treating SKOV3 cells by this NP increase cytotoxicity, and xenograft mice models showed targeting and accumulation of this NP in tumor tissues [44].

NP-drug conjugates (NDCs) are more effective than antibody-drug conjugates (ADCs) for loading monomethyl auristatin E (MMAE) in OC therapy. So, the results were very promising in the level of in vitro and in vivo, and inhibition of tumor growth and cytotoxicity in a patient-derived xenograft model of platinum-resistant OC is twice as much in comparison with CIS administration [45].

Depolarization of mitochondria and augment the level of ROS that cause apoptosis and finally, cytotoxicity in tumor cells are other results of administration NPs individually or in combination with chemotherapy drugs. So, Gold NPs encapsulate theaflavin (tea-extracted polyphenols) (AuNP@TfQ) as an apoptosis inducer in tumor cells. Anti-cancer activity of AuNP@TfQ enhanced by pristine theaflavin oxidation to its quinone derivative on the surface of gold NPs. The entrance of AuNP@TfQ into the PA-1 cells takes place through endocytosis. In this study caspase-3, Bax, Bad, BID, and BIM as pro-apoptotic markers and Bcl-2 and Bcl-was anti-apoptotic markers were evaluated [46].

But NPs individually can lead to cytotoxicity and apoptosis in tumor cells too. Gurunathan and colleagues proposed Ag NPs and ZnO NPs with a broad range of application in biomedical was used to treat OC individually and synergy with gemcitabine (GEM). Results represented a reduction in cell viability in a dose and time dependent manner and DNA double-strand break due to the overproduction of ROS and mitochondria dysfunction in both experiments [47, 48].

3.3 Gene delivery

Herein, we focused on some gene delivery based examples used for OC treatment. NPs due to their properties are used as a vehicle for delivery of different nucleic acids such as siRNA, miRNA and shRNA. Increasing cytotoxicity by inducing apoptosis and suppressing tumor growth and volume are the common results obtain via silencing or downregulating oncogenes. Modifying NPs with ligands for improving delivery is also utilized in this technique.

3.3.1 NPs for siRNA delivery

Using siRNA in oncotherapy because of low toxicity, high effectiveness and specificity is a terrific choice. To improve the efficiency and overcome the problem such as degradation by RNase and lack of the ability to penetrate the membrane cells, is better not to use naked siRNA. To facilitate the capability of siRNA and presence in proper concentration for silencing or downregulating of oncogenes, gene delivery systems play an essential role. Polymeric and lipid-based NPs are the most usable carriers for siRNA. Polymeric NPs especially PEI, PEG and chitosan with a positive charge easily bind to oligonucleotides with a negative charge through electrostatic interactions. While lipid NPs such as liposomes encapsulate siRNA in its aqueous core [30]. Polyethylenimine-graft-polycaprolactone-block-poly(ethylene glycol) modified FA (hyPEI-g-PCL-b-PEG-FA) is one of the examples polymeric NPs was used for transfer siRNA to SKOV-3/LUC cells with a high level of FRα [49].

Another protein targeted is TWIST that responsible for epithelial-mesenchymal transition and is related to angiogenesis, metastasis and drug resistance. So, using siRNA against TWIST protein conjugated with mesoporous silica nanoparticles (MSN-HAs) (siTWIST-MSN-HA) for delivery to epithelial OC (EOC) cells. HA help to specific target delivery to CD44 positive cells (A2780R cells). Moreover, due to the positive charge of PEI, the surface of MSN modified that, to improved attachment of the siRNA (negative charge) and HA to the amine groups in the PEI. By down-regulation of TWIST protein, OC cells become sensitive to drugs such as CIS. In vivo studies showed inhibition in tumor growth, and evaluating TWIST,

Vimentin, N-Cadherin, and E-Cadherin tumor mRNA as EMT markers in mice that were treated by siTWIST-MSN-HA + CIS indicated great result in combination therapy [50].

Protein kinases are a considerable target for gene delivery for cancer treatment, so knockdown of p70 S6 kinase (p70S6K) is necessary for a decrease in migration, invasion and proliferation of OC stem cells (in vitro) and reduction in tumor growth and metastasis (in vivo). In this regard, p70S6K siRNA by G6 dendriplex NPs, that protect it from degradation, transfer to OC stem cells. Also, knockdown of p70S6K via this NP complex can inhibit the stemness and self-renewal properties of cancer stem cells (**Figure 5**) [51].

Kinesin spindle protein (KSP) is another gene, that by silencing, cell cycle arrest in mitotic phase and apoptosis happened in cancer cells. So, for transfection of KSP siRNA into the SKOV3 cells, PEGylated DC-Chol/DOPE lipoplexes were prepared. These NPs are caused to enhance accumulation in tumor tissue for suppression of tumor growth and decrease damage to kidneys and liver in SKOV3 tumor-bearing mice [52].

Besides, growth and metastasis of tumor cells regulate by angiogenesis, so develop an NP with anti-angiogenesis property, plays an essential role in the treatment of OC. HA attached to chitosan NP enclose PLXDC1 siRNA for inhibition PLXDC1 as an angiogenesis gene. HUVEC and MOEC cells via expression CD44 have the potential to absorbed these nanocarriers and induced cytotoxicity and apoptosis. Administration HA-CH-NP/siRNA by A2780 tumor-bearing mice demonstrated antitumor characterization that causes to suppressing tumor growth and volume [53].

In another method for gene delivery, NPs were designed to transfer two siRNA to cancer cells to obtain the higher output. For instance, PLGA NPs loaded MDR1 and BCL2 siRNA were prepared. Silencing both genes simultaneously have an extraordinary effect on resistant OC cell sensitivity to PTX and CIS. In vitro experiments

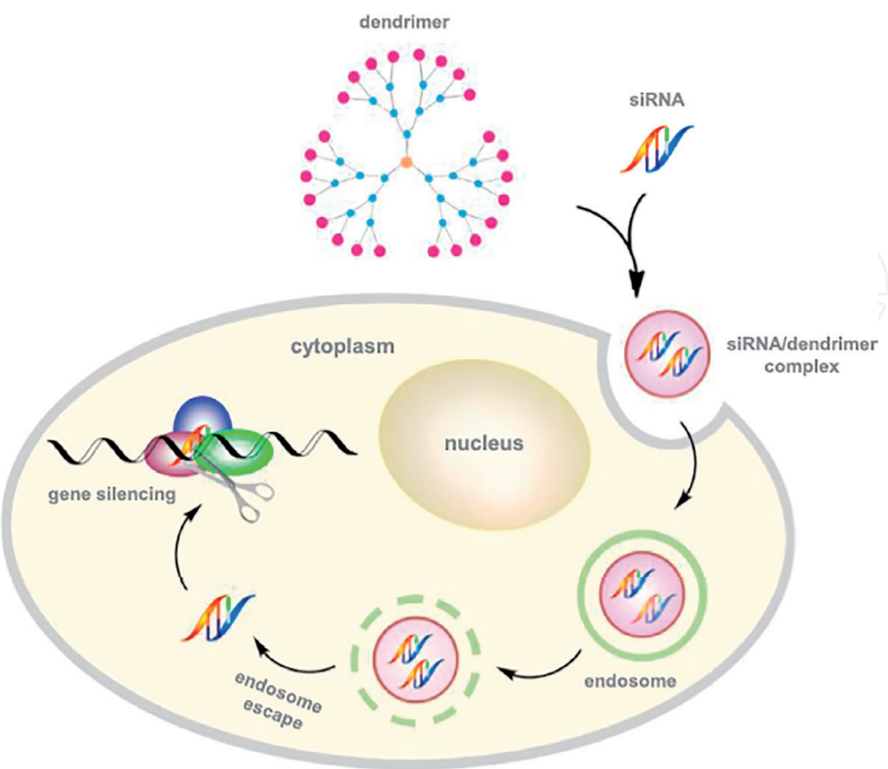

Figure 5.
Targeting p70S6K with dendriplex nanoparticles inhibit stemness and metastatic properties of OC cells. This figure was obtained with permission from [51] under the terms of creative commons CC BY license.

implement on the PTX-resistant and CIS-resistant, SKOV3-TR and A2780-CP20 cells respectively. The observations indicated an increment in cellular uptake that induces cell death by apoptosis and necrosis [54].

3.3.2 NPs for shRNA delivery

shRNA is a stem-loop RNA that in comparison with siRNA cause prolong gene silencing and highly effective. In the following, 2 examples of this procedure have been brought. PEG NPs with a peptide of FSH β 33-53 for specific target delivery encapsulate shRNA for silencing growth-regulated oncogene α (gro-α) (FSH33-G-NP). Internalization in FSHR positive cells like HEY cells is more. FSH33-G-NP decrement cell proliferation, invasion and migration and also in vivo experiments showed antitumor activity [55]. Also, overexpression of pin1 is related to cancer malignancy by regulating oncogenes and tumor suppressor genes, so silencing of pin1 can inhibit the tumor growth in a syngeneic mouse model and induce apoptosis in OC cells. Proteasome-dependent degradation of Pin1 happened via liposome-based NPs that were modified by cyclodextrins for shRNA delivery (**Figure 6**) [56].

3.3.3 NPs for miRs delivery

Micro RNAs (miRs) are short and non-coding RNAs that modulate gene expression at the level of post-transcriptional. The existence of them is necessary for the regulation of cell metabolism, differentiation, proliferation, and apoptosis. But sometimes, dysregulation and improper expression of miRs (oncomiRs) are related to the early and advanced stages of cancers, so, anti-miR delivery for downregulating oncomiR is an anticancer strategy. A high level of miR-21 is related to the incidence of many cancers including OC. In order to improve cancer therapy porous silicon NPs that were modified by MAL-PEG-SVA enclosed anti-miR-21 (LAN) to target OAW42 ovarian cells. In this study, CREK peptide as a control peptide for no targeting activity in cell culture and CGKRK peptide for displaying tumor-homing and tumor penetrating properties were analyzed for comparison. Findings illustrated a decrease in cell viability due to apoptosis by evaluating caspase-3, and also, COV-318 xenograft tumors subcutaneously transplanted into nude mice after treatment represented the higher accumulation of NPs in tumor tissue that lead to inhibition effect on tumor growth and volume [57].

3.4 Combination of gene and drug delivery

The combination of gene and drug delivery is another factor to enhance the chance of success in oncotherapy. For example, Both paclitaxel (PTX) and focal adhesion kinase (FAK) siRNA loading HA-labeled poly(d,l-lactide-co-glycolide) NPs (HA-PLGA-NP-PTX+FAK siRNA) were used for ovarian oncotherapy. Tumor cells due to the presence of CD44 obtain more HA-PLGA-NP-PTX+FAK siRNA which decreases cell viability by inducing apoptosis in both SKOV3-TR and HeyA8-MDR (multidrug resistance) cells. Knockdown of AKT pathway that has a role in metastasis and drug resistance, have occurred by FAK siRNA [58].

In another experiment, a novel combination of chemotherapy and gene therapy for A2780DDP cells and xenograft nude mice model was developed. Platinum(IV)–azide complexes (Pt(IV) prodrugs) and the siRNA of c-fos (si(c-fos)) embedded in a photoactivatable polymeric NP. Pt(IV) prodrugs are nontoxic in dark but after mild light (blue light) irradiation, it released the Pt(II) drug that has cytotoxic activity. This nano vehicle has high drug loading properties and extraordinary stability that lead to cytotoxicity and antitumor characterization (**Figure 7**) [59].

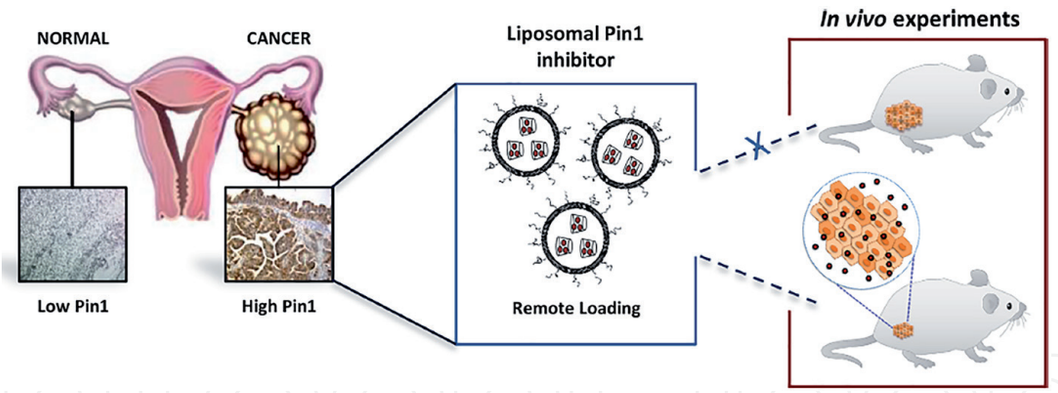

Figure 6.
Anti-Pin1 and cyclodextrins loaded to liposome as a new therapy for OC. This figure was obtained with permission from [56] under the terms of creative commons CC BY license.

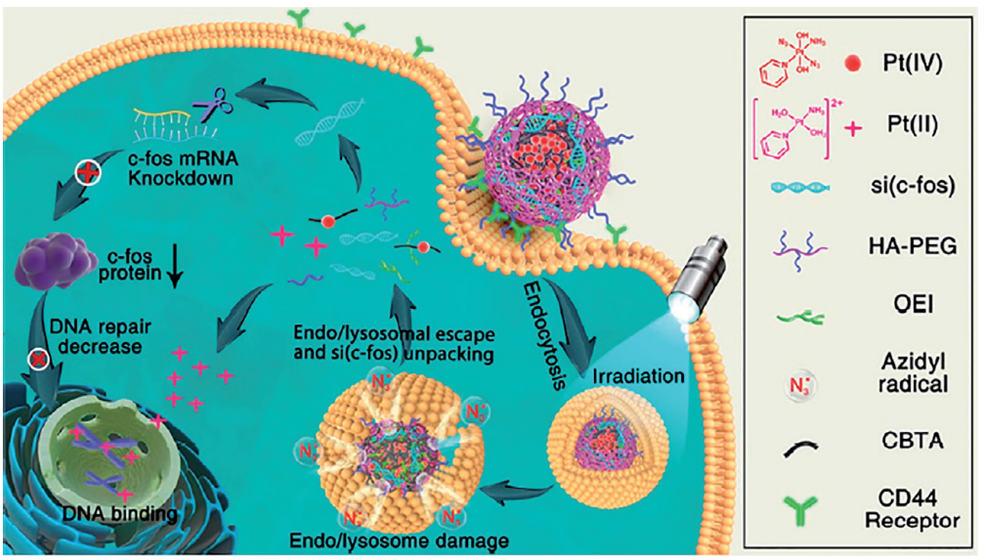

Figure 7.
Photoactivatable polymeric nanoparticles as a gene and drug delivery for platinum-resistant OC. This figure was obtained with permission from [63] under the terms of creative commons CC BY license.

Furthermore, A2780R cells treated by two separate NPs were developed for the delivery of drug and gene. CIS resistance leads from overexpression of miRNA-21 in OC. So, anti-miRNA-21 by PEGylated poly(lactic-co-glycolic acid) NPs which decorated with AS1411 antinucleolin aptamer for developing target delivery (Ap anti-miR-21-NPs) and NPs contain CIS (Ap–CIS–NPs) deliver to A2780R cells. It is caused to the reduction in drug resistance by inhibiting miRNA-21 and increased mortality via induction apoptosis [60].

4. Gas plasma based therapy for ovarian cancer oncotherapy

4.1 Gas plasma: key features and applications

Gas plasma is a novel technology with potential and actual applications ranging from energy and water to food sciences [61]. Management of gas plasma effects on biological objects is related to different factors including charged particles, electric fields, UV radiation, and RONS. These chemical and physical factors are involved in combination or multimodal forms, provide a solution for a variety of medical applications [62] (**Figure 8**). Cancer therapy, wound healing, virus inactivation,

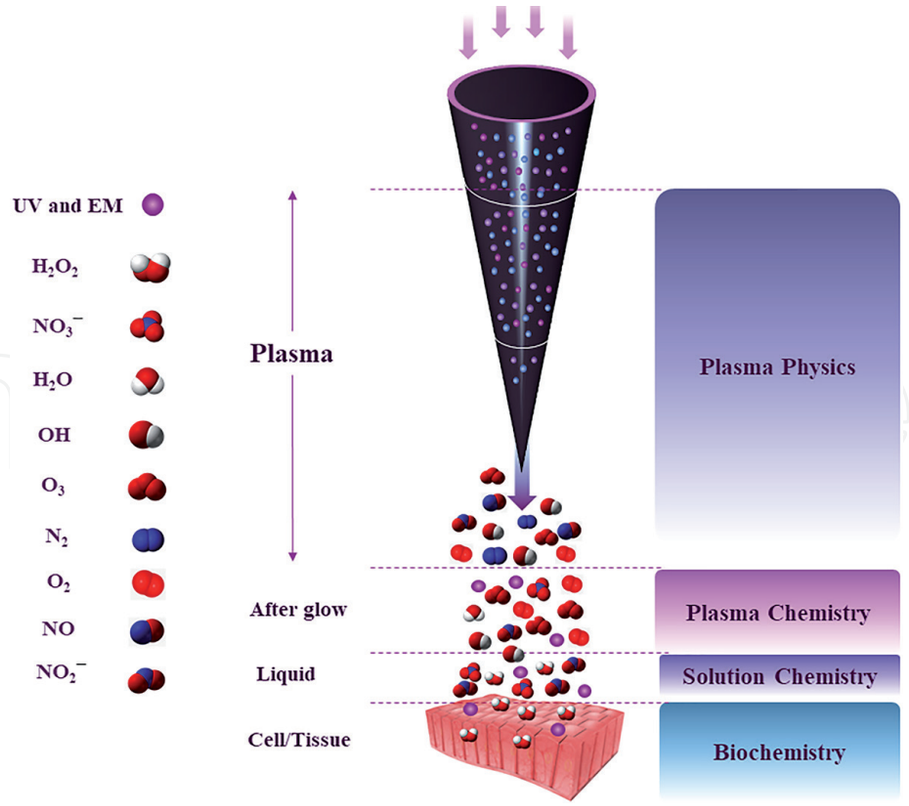

Figure 8.
The key role of reactive agents from generation in the plasma to interaction with the biological objects.

biofilm removal, dentistry, and ophthalmology, as well as cosmetic uses, are some of the applications of plasma in medicine. It is now clear that plasma is a promising therapeutic candidate for the multivariate condition of cancer [63, 64].

Recent studies revealed, gas plasma oncotherapy provides insights into the wide context challenging of cancer treatment through physical and chemical effects. Until now, the underlying mechanisms of plasma action were ascribed to RONS, but more recently, the role of physical factors (UV and EM) is also emphasized [62, 65]. These cocktails inducing dose-dependent effects, redox flux increase to cells, flexibility in use, multimodality nature, and the mild effect that are primary features of gas plasma [8]. Also, these unique physicals, chemical and biological properties have a high potential to act synergistically and will be crucial to the achievement of selectivity for cancer cells, enhancing cancer chemosensitivity, stimulation of the immune system, elimination of cancer stem cells, halting cancer metastasis as medical features of gas plasma oncotherapy [6, 63]. Thus, plasma as an alternative effective technology eliminates some of the most important undesirable consequences and side effects of common treatments. The great antitumor impact of plasma for all types of cancer have been reported [66].

4.2 Direct and indirect plasma treatment: role of the device and liquid

Plasma treatment is divided into two general direct and indirect modalities in order to offer new solutions to its increasingly diverse range of applications, as well as to cover the requirement related to them. In addition to exposing biological objects to plasma radiation, another method was developed. In the indirect treatment modality that has known as plasma activated liquid, the solution is exposed to plasma irradiation and then is added to the biological target [15, 67, 68]. It seems like the direct method is suitable for superficial tumors, but for peritoneal tumors,

the indirect method or plasma-activated liquid is a good option and can be used as innovative technology. By ignoring the unknown complexities of plasma liquid interaction, the RONS play a dominant role in PAL.

Atmospheric Pressure Plasma Jets (APPJ) and volume and surface Dielectric Barrier Discharge (DBD) are three configuration types of common plasma devices used for biomedical application. Regarding the feeding gas, noble gases, air, nitrogen, or a combination of that, are utilized for the generation of plasma depending on the configuration used [69, 70]. Toward the APPJ, the DBD seems to be appropriate for the production of plasma-activated liquid due to the larger volume of exposed solution [69].

Culture mediums (DMEM, RPMI, alpha-MEM), Phosphate-buffered saline (PBS), and Ringer's solution have been reported as an exposed solution for PAL generation. Currently, all three types of solutions are used to produce PAL. As it was previously mentioned, aside from plasma device and process parameters, the compositions of the liquid have a pivotal role in the plasma action [15, 71]. It is appropriate to use solutions that have less interaction with plasma and do not change their function. However, it is well established that the sensitivity of cells to culture conditions is another limitation of this method and many cells are destroyed by changing the culture medium. Taken together, further research in this regard is very vital.

4.3 Ovarian cancer oncotherapy through gas plasma: selectivity, restores chemotherapy sensitivity, and metastasis inhibition

OC, colorectal cancer, pancreatic/appendiceal cancer, stomach cancer, peritoneal mesothelioma, and primary peritoneal cancer are the most common cancers that cause peritoneal carcinomatosis. In recent years, treatment strategies for these cancers, improved by combining several existing methods. [72]. Nevertheless, peritoneal carcinomatosis treatments are ineffective and require new multiple strategies that provide targeted drug delivery on a large scale.

OC the most important type of cancer in the cancer cells response discovering process to the plasma. Albeit the number of relevant studies examining OC with gas plasma is limited compared to other cancers. Most studies have been examined the selectivity of gas plasma oncotherapy on cancer or healthy cells. Regarding chemotherapy resistance, the impact of plasma on acquired and intrinsic resistance cells also have been investigated. Besides, various evidence suggests that gas plasma plays a crucial role in OC by mediating several genes involved in proliferation, apoptosis, migration, and metastasis.

The selectivity mechanism of gas plasma oncotherapy has been demonstrated in our previous work [73], briefly, plasma-derived H_2O_2 and NO_2^- produce primary $^1O_2$, thereby inactivating some of the catalase of cancer cells. Then, Due to the differences between healthy and cancerous cells, cell-based secondary $^1O_2$ generation is high, and therefore more catalase is inactivated. So, H_2O_2 with penetrating the cells through aquaporin causes depletes GSH or activities Hypochlorous acid (HOCl) and $^{\bullet}NO/ONOO^-$ signaling that leads to caspase-mediated cell death [74] (**Figure 9**).

Here, we outline the existing studies about the application of gas plasma and the mechanisms responsible for their expression strictly in OC. PAL has great potential to act as an innovative approach and overcome multiple biological barriers and treatment challenges in peritoneal cancers. Thus, PAL is a commonly used therapeutic option in this chapter. Also, it seems Ringer Lactate solution will be a proper liquid for future plasma activated liquid and has direct anti-cancer activities.

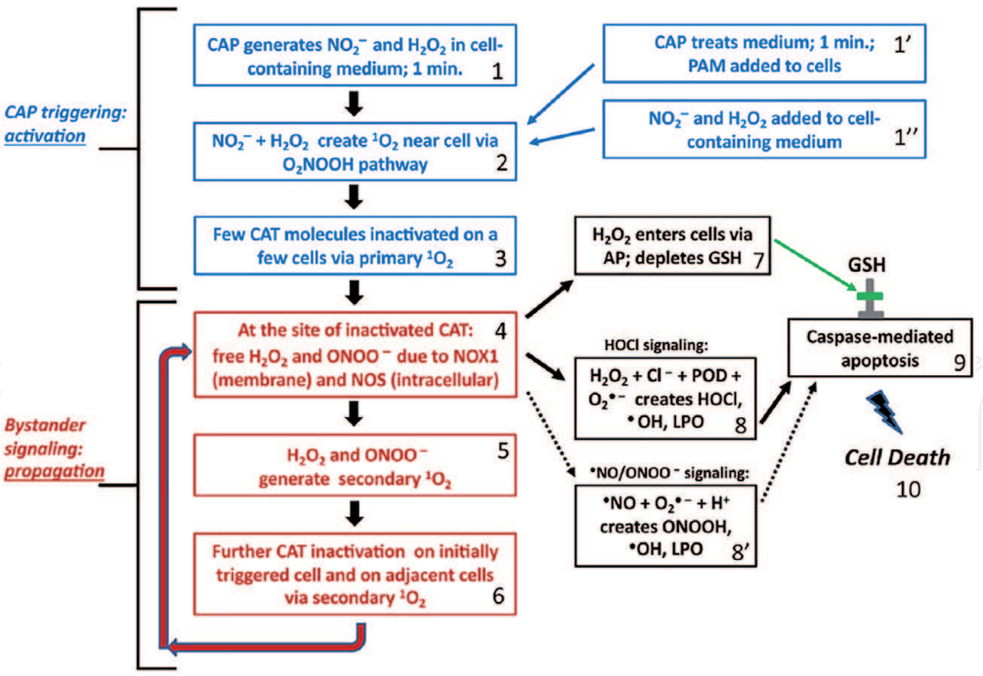

Figure 9.
Flow chart of major steps in CAP leading to selective apoptosis of tumor cells. Step 1: CAP generates NO_2^- and H_2O_2 in cell containing medium for 1 minute. Alternatively, CAP is used to treat medium, creating PAM (step 1′). Defined concentrations of NO_2^- and H_2O_2 containing medium are used in reconstitution experiments (step 1″). Step 2: NO_2^-- and H_2O_2 create primary $^1O_2$ near cells following O_2NOOH pathway, as described in reference. Step 3: Few catalase molecules on a few cells are inactivated due to primary $^1O_2$ near cells. Step 4: At the site of inactivated catalase, H_2O_2 and $ONOO^-$ (generated through NOX1 and NOS) are no longer decomposed. Step 5: The reaction between H_2O_2 and $ONOO^-$ is leading ultimately to secondary $^1O_2$. Step 6: This additional $^1O_2$ leads to further catalase inactivation and the process cycles back to step 4. Step 7: Increased H_2O_2 resulting from catalase loss from secondary $^1O_2$ leads to H_2O_2 entering cells via aquaporins, leading to antioxidant glutathione depletion. Step 8: In parallel with step 7, increased H_2O_2 resulting from catalase loss from secondary $^1O_2$ also leads to HOCl generation by peroxidase, in the presence of Cl^-. The interaction between NOX1 derived $O_2^{\bullet -}$ leads to $^\bullet OH$ formation near the cell membrane and lipid oxidation. Step 8′: If HOCl signaling is suppressed, an alternative $^\bullet NO/ONOO^-$ signaling can also lead to lipid peroxidation. Step 9: If both lipid peroxidation and glutathione depletion occur, then caspase-associated apoptosis can take place, finally leading to cell death. Steps 1–3 correspond to CAP triggering or activation of a few cells, thereby initiating propagating bystander signaling in steps 4–6. Steps 7–9 are the steps that lead to the final cell apoptosis. These steps are activated only if the repeated performance of steps 4–6 has caused a sufficiently high degree of catalase inactivation for reactivation of HOCl or $^\bullet NO/ONOO^-$ - mediated apoptosis-inducing signaling. This figure was obtained with permission from [74] under the terms of creative commons CC BY license.

Selectivity towards cancer cells, chemotherapy-resistance elimination, restore sensitivity to chemotherapy, inhibition of metastasis, and more recently the possible mechanism of plasma action has been achieved in these studies.

Gas plasma effects on OC were first examined on two human epithelial ovarian carcinoma cell lines, SKOV3 and HRA and normal human fetal lung fibroblast cell lines, WI-38 and MRC-5. Nonequilibrium atmospheric pressure plasma (NEAPP) was utilized to assess toxicity and proliferation inhibition. Cell proliferation, flow cytometry, western blot analysis along with pH, temperature, and volume of the medium before and after plasma treatments were evaluated. NEAPP selectively targets two cancer cells and induces apoptosis in them, while normal cells were not damaged. Although the authors do not address the mechanism of action, they assume a pivotal role in the process of plasma application for UV radiation, charged particles, and free radicals such as reactive oxygen species (ROS). Also, pH, temperature, and volume of culture medium did not affect by plasma irradiation [75].

Given that compositions of culture medium act as key mediators of biological responses triggered by gas plasma and can affect results. In a study by Boehm et al. hypothesized that instead of a culture medium, PBS to be used. The solution

compounds used can play an important role in investigating the cytotoxic effect of plasma on HeLa and CHO-K1 cell lines. They found that the surrounding milieu and the presence of anti-oxidants such as pyruvate in PBS can change and influence the generation of H_2O_2 and related results [76].

In addition, cell proliferation and cell motility of SKOV-3, OVCAR-3, TOV-21G, and TOV-112G cells as OC cells investigated by direct and indirect exposure to gas plasma. In accordance with other studies, CAP and PAM have similar cytotoxicity effects on the mentioned cell lines. Also, dose-response effects depending on cell type and exposure time [77].

Bekeschus and colleagues attempt to insight the interaction of gas plasma with tumor microenvironment and immunomodulatory properties. Accordingly, human OC cell lines OVCAR-3 and SKOV-3 as well as human THP-1 monocytes have been used to examined gas plasma effect. The results indicate that plasma can trigger cell death in a caspase 3/7 independent and dependent manner for OVCAR-3 and SKOV-3 OC cell lines, respectively. Also, tumor cell-induced monocyte/macrophage phenotype reverted by plasma therapy [78].

Owing to clinical facts and desirability of Ringer's Lactate solution in comparison to the culture medium, Bisag et al. investigated the efficacy of plasma-activated Ringer's Lactate solution (PA-RL) on OC cell lines (SKOV-3 and OV-90) and non-cancer cells (HOSE cell line and two lines of immortalized fibroblasts (F1 and F2)). It was the first time that a multiwire plasma source without needing technical gas was used to activate a solution with a volume of 20 mL. Chemical characterization and measurement of long-lived RONS concentration in different PA-RL dilutions were performed. Results confirm that PA-RL showed selective cytotoxicity towards cancer cells, whereas normal cells remained unaffected. These observations are related to the pH and H_2O_2 and NO_2^- in the PA-RL [79].

4.3.1 Gas plasma restores chemotherapy sensitivity in chemoresistance OC cells

Improving the performance of conventional treatments is a significant part of oncotherapy. The cancer treatment new strategy requires advantages over conventional treatment methods. This is achieved by exploring new approaches to restore sensitivity to chemotherapy. Thus, gas plasma oncotherapy to introducing as an innovative oncotherapeutics agent should have been effective than conventional drugs. Besides, able to re-sensitize chemotherapy resistance cells to chemotherapeutic agents while maintaining selective effect toward normal and cancer cells.

Combination effects of CAP and PAL with conventional therapy like chemotherapy, radiation therapy, pulsed electric fields, nanoparticles, and plant origin have been discussed in recent years to improve the effectiveness of these methods. Here we also report the last work about the combination of chemotherapy drugs with gas plasma that has been conducted for OC treatment.

In a most recent research, to develop an innovative strategy for OC treatment, Rasouli et al. focused on the selective effect of gas plasma oncotherapy and eliminating chemotherapy resistance. For this purpose, hypodiploid human cell line, A2780 CP, SKOV-3 as OC cell lines, and Granulosa cells (GCs) as normal primary cells were used. As shown in **Figure 10**, we further utilized several treatment modalities including chemotherapeutic agents (carboplatin (CAR), PTX, a combination of CAR and PTX), gas plasma (direct exposure (CAP), plasma activated medium (PAM)), and combination of PAM whit chemotherapy drugs. IC_{50} of mentioned cells and selectivity index of cancer cell lines were obtained. Our results demonstrated the calculated selectivity indices of the CAR and PAM for A2780 CP, SKOV-3 smaller than the three that specified for the interesting selectivity index. Among all plasma treatment methods, PAM 10% FBS induced high selectivity

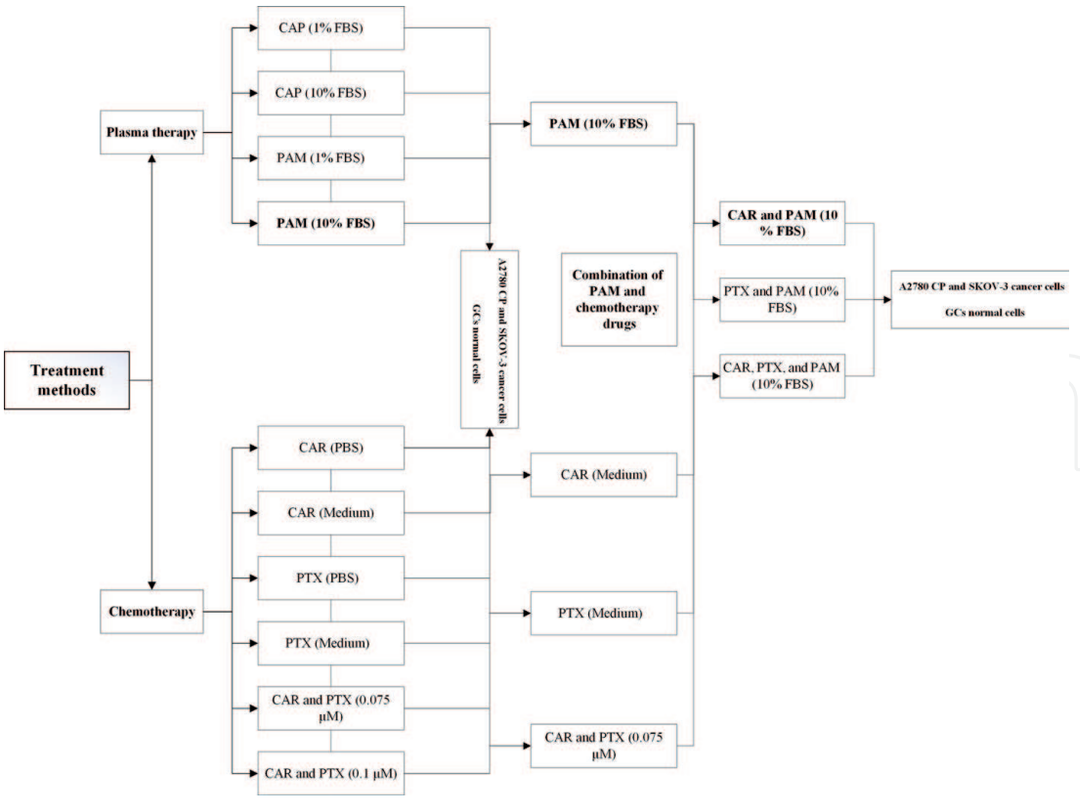

Figure 10.
Diagram of treatment methods in this study. CAP (cold atmospheric plasma), PAM (plasma activated medium), PTX (paclitaxel), CAR (carboplatin). All treatment methods were performed on three A2780 CP, SKOV-3, and GCs cells.

towards OC cells. Also, selectivity performance of other plasma therapies such as CAP 1% FBS, CAP 10% FBS, and PAM 1% FBS compared with chemotherapy drugs were desirable. According to the carboplatin resistance of cancer cells, it was a very interesting result [19].

In another part of this study, to improve the performance of chemotherapy drugs, co-treatment of these agents with PAM was investigated. Although PAM improves efficacy and selectivity indices of CAR and PTX but induces high selectivity in conjunction with CAR. In general, we concluded that PAM alone and simultaneous with CAR selectively induced apoptosis in chemotherapy-resistant OC cells accompanied with high expression of P53, BAX, and CASP-3. The novelty of PAM and combination treatment led to developing a new trend in OC oncotherapy associated with produced RONS (H_2O_2, NO_2^-, NO_3^-), reduced pH in plasma activated medium and physical factors such as UV and electric field [19].

Assuming gas plasma oncotherapy is closer to the therapeutic facts, Utsumi et al. used NEAPP-activated medium (NEAPP-AM) as an intraperitoneal (IP) treatment modality. To this end, for the first time, NOS2 and NOS3 as chronic paclitaxel/cisplatin-resistant OC cells and xenografted tumors in a mouse model were investigated by NEAPP-AM. Also, they assessed the role of ROS or their scavengers in NOS2 and NOS3 OC cells. Given fact that NOS2 and NOS3 are acquired resistance to paclitaxel, the study was a very crucial role in plasma oncotherapy research. The results revealed PAM has an interesting cytotoxicity effect on chemo-resistant OC cells. Besides, PAM can induce an anti-tumor effect on the xenograft model. There is no difference between direct and indirect treatment, but due to the benefits that PAM creates the authors suggested it as future intraperitoneal administration [80].

Clear cell carcinoma (CCC) of the ovary is a rare histological subtype of epithelial OC (EOC), has the worst prognosis and exhibits high rates of recurrence

and low chemosensitivity. Therefore, developed a novel approach to combat CCC is critical. Hence, Utsumi et al investigated the influence of gas plasma on TOV21G as a CCC cell line by NEAPP-AM. The ES-2, SKOV3, and NOS2 as other EOC cell lines and omentum derived human fibroblastic cells (OHFC) and human peritoneal mesothelial cells (HPMC) as normal cells were examined. The study demonstrated that PAM with high selectivity induces apoptosis in CCC cells which is resistant to chemotherapy. Also, ROS produced by PAM in cancer cells were considered as a selectivity factor [81].

E-cadherin has pivotal roles in epithelial cell behavior, tissue formation, and suppression of cancer and is a critical part of epithelial cell adhesion and epithelial-to-mesenchymal transition (EMT). Furthermore, transforming growth factor-β1 (TGF-β1) is a multifunctional growth factor that plays a crucial role in chronic inflammation in various tissues and regulates several cellular processes, including cell cycle arrest, differentiation, morphogenesis, and apoptosis. From this viewpoint, Wang et al. focused on various factors such as cell numbers and the morphological characteristics of cells, that are thought to be effective in the interaction of plasma and cells. Four human OC cell lines, OVCAR-3, TOV21G, NOS2, and ES-2 used to examine differences in responses to gas plasma oncotherapy through direct and indirect irradiation. The point to consider was the different sensitivities of the used cancer cells to conventional chemotherapy drugs. They concluded compared with the other two cell lines, TOV21G and ES-2 cells were drastically sensitive to PAM treatment, as well as, sensitivity to PAM therapy in OC cells is related to their number and morphology. Having a negative impact of cell density on cell proliferation inhibition rate (PIR) is more evident in OVCAR-3 and NOS2 cells. Regarding cell morphology and PAM sensitivity, low E-cadherin expression was suggested as a factor for more PAM sensitivity. Also, TGF-β1 with inducing mesenchymal morphologic change can sensitize cancer cells to PAM [82].

OC is one of the gynecological malignancies that penetrates the peritoneum. That means cancer developed a spread of largest volume and treatment of it is challenging. Intraperitoneal therapy is a concept utilized in these cases to focused

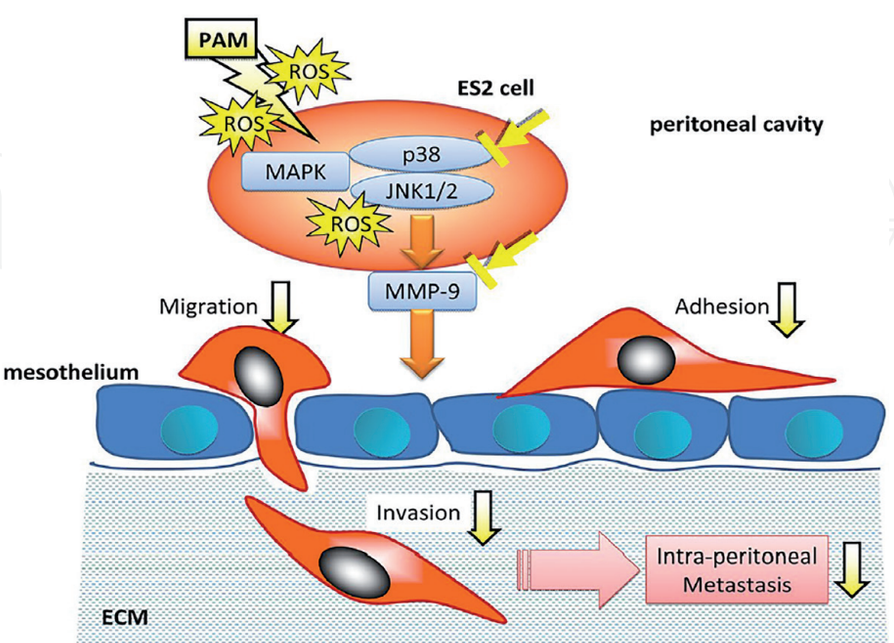

Figure 11.
Mechanisms of the anti-metastatic effect of PAM. ROS in PAM diffuses into ES2 cells and down-regulates MMP-9 expression via inhibiting of MAPK pathway, suppressing cancer cell adhesion, migration and invasion onto mesothelial cells lining the peritoneal cavity. Finally, PAM prevents intraperitoneal metastasis. This figure was obtained with permission from [83] under the terms of creative commons CC BY license.

on local delivery. For this purpose, Nakamura et al. introducing PAM intraperitoneal therapy as an innovative option for OC oncotherapy. The experiments were designed to assess the inhibit metastasis effectiveness of PAM on OC ES2, SKOV3, and WI-38 cell lines in vitro and ES2 in in-vivo levels. They mentioned that PAM treatment suppressed ES2 cell migration, invasion, and adhesion while cell viability changes were negligible [83].

Most importantly, PAM inhibited peritoneal dissemination of ES2 cells, resulting in prolonged survival in an in-vivo mouse model of intraperitoneal metastasis. Furthermore, the evaluated underlying mechanism revealed PAM inhibited the phosphorylation of JNK1/2 and p38 MAPK and prevented the MAPK pathway activation. Besides, PAM was decreased MMP-9 expression [83] (**Figure 11**).

5. Conclusion and perspective

Despite rapid advancements for OC oncotherapy, our understanding of the cause and management of OC is limited. Cancer cells become resistant to conventional chemotherapy and increasing the concentration of drugs just enhances the side effects, and does not cause any improvement in recovery. Besides, approved oncotherapy drugs for clinical and preclinical administration, faces several obstacles to treatment. Introducing combined therapeutic strategies such as nanoparticle and gas plasma that used the synergizing advantage of these approaches holds great potential for future combination or multimodal OC treatment.

The bioavailability property of NPs enhances their efficacy in drug loading and protects them from physiological barriers. To provide a suitable platform for clinical trials, it is very crucial to analyze the NPs safety at the level of in vitro and in vivo. Therefore, the reviewed NPs need more experiments in the level of in vivo for entrance into the clinical arena. Furthermore, gas plasma is not considered as the therapeutic strategy for modern medicine unless focused studies are performed on the design and manufacturing of simple, accurate, standard, and low-cost plasma devices.

While the identification of the underlying mechanism of each gas plasma and nanocarriers technology is under debate, promising observations open up interesting avenues for them as an emerging candidate in future oncotherapy. Independently from action mechanisms of gas plasma and nanoparticles, these therapies rely on the selective ability of them to discriminate between healthy cells and cancerous ones.

Indeed, gas plasma and nanoparticles as novel biomedical fields need funding from a wide range of government agencies and international research centers to be specifically targeted towards research at the intersection of these disciplines and resolve modern challenges such as cancer. Finally, we hope that this chapter will enhance collaboration between researchers in interdisciplinary research fields including physics, chemistry, biology, oncology, and medicine, and provide the needed interplay to address current challenges in OC management. Aside from providing new knowledge on molecular mechanisms in the mentioned modalities, to overcome the failure of oncological ovarian treatment, synergizing of innovative therapeutic approaches can be useful.

Collectively, our strategy potentially opens a new and accessible approach and led to addresses several cancer challenges. As a future direction, we hope to combine new approaches with conventional treatments to obtain finer modalities, improve the efficiency of each of them, and resolve oncotherapy challenges.

Conflict of interest

The authors have no conflict of interest to declare.

Acronyms and abbreviations

RONS	Reactive Oxygen and Nitrogen Species
DDS	Drug delivery system
GDS	Gene delivery system
CTX	Chemotherapy
ECT	Electrochemotherapy
RT	Radiotherapy
PDT	Photodynamic Therapy
HT	Hyperthermia
UV	Ultraviolet
NPs	Nanoparticles
miRNA	microRNA
shRNA	Short Hairpin RNA
AONS	Antisense Oligonucleotides
siRNA	Small interfering RNA
Tf	Transferrin
R8	Octaarginine
DOX	Doxorubicin
HA	Hyaluronic acid
CIS-pARG-HA NPs	Cisplatin-loaded polyarginine-HA NPs
PIPAC	Pressurized Intraperitoneal Aerosol Chemotherapy
FRα	Folate Receptor α
FA	Folic Acid
NE	Nanoemulsion
DTX	Docetaxel
TQR	Tariquidar
pHSL	pH-Sensitive Liposome
CHEMS	Cholesteryl Hemisuccinate
DOPE	1,2-dioleoyl-sn-glycero-3-phosphoethanolamine
MNPs	Magnetic NPs
ETB	Erlotinib
MRI	Magnetic Resonance Image
GO-PVP-NPs	Polyvinylpyrrolidone functionalized Graphene Oxide NPs
CB	Cubosomes
EGFR	Growth Factor Receptor
PROC	Platinum-Resistant Ovarian Cancer
Wtmn	Wortmannin
CIS	Cisplatin
NDCs	NP-Drug Conjugates
ADCs	Antibody-Drug Conjugates
MMAE	Monomethyl Auristatin E
GEM	Gemcitabine
PEI-g-PCL-b-PEG-FA	Polyethylenimine-graft-polycaprolactone-block-poly(ethyleneglycol) modified FA
EOC	Epithelial Ovarian Cancer
p70S6K	p70 S6 kinase
KSP	Kinesin Spindle Protein

gro-α	Growth-Regulated Oncogene α
miRs	Micro RNAs
PTX	Paclitaxel
FAK	Focal Adhesion Kinase
MDR	Multidrug Resistance
DBD	Dielectric Barrier Discharge
PBS	Phosphate-buffered saline
HOCl	Hypochlorous acid
NEAPP	Nonequilibrium atmospheric pressure plasma
ROS	Reactive Oxygen Species
PA-RL	Plasma-Activated Ringer's Lactate solution
GCs	Granulosa Cells
CAR	Carboplatin
PAM	Plasma Activated Medium
NEAPP-AM	NEAPP-Activated Medium
IP	Intraperitoneal
CCC	Clear Cell Carcinoma
EOC	Epithelial Ovarian Cancer
OHFC	Omentum Derived Human Fibroblastic Cells
HPMC	Human Peritoneal Mesothelial Cells
EMT	Epithelial-to-Mesenchymal Transition
TGF-β1	Transforming Growth Factor-β1
PIR	Proliferation Inhibition Rate

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