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Gas plasma for cancer treatment: Current insight and future trends

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Abstract
Cancer is the leading cause of mortality worldwide and facing the healthcare system with major challenges due to the inadequate efficacy of current onco-therapeutic agents. Compared to the current therapeutic modalities, gas plasma oncotherapy leading to outstanding outcomes owing to its multimodal nature and adjustable dose nature. Reactive agents are produced in the interaction of plasma plume with air, liquid, and cells, resulting in dose-dependent selective cell deaths. Gas plasma oncology aims to utilize medical gas plasma for cancer treatment, which exhibits a great anti-cancer platform. In this review, gas plasma oncotherapy from main indicators to state-of-the-art topics comprehensively is presented. Moreover, we focus on the nexus between plasma-generated chemical and physical effects and desirable biological responses and discuss the precise role of these agents in the treatment procedures. Additionally, plasma dose as dependent on the input parameters and process factors is defined. Molecular and selectivity mechanisms of gas plasma oncotherapy are discussed in detail. Finally, the current challenges in gas plasma oncotherapy are presented and future trends are discussed.

Keywords
Cancer, gas plasma, reactive oxygen and nitrogen species (RONS), selectivity.

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1. Introduction

Cancer is becoming a chronic disease and causes high mortality and morbidity rates worldwide, so that it is estimated more than 1600 Americans will die per day from cancer in 2021 [1]. Cancer remains a global challenge and the current situation of oncotherapy has created a major problem for the health system. Surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, stem cell or bone marrow transplant, and hormone therapy, or a combination of these, are used for cancer treatment depending on the type of cancer and its grade [2].

The majority of chemotherapy drugs, which have diverse chemical structure, can target cells at various cell cycle phases and causes cell deaths. Alkylating agents, antimetabolites, anti-tumor antibiotics, topoisomerase inhibitors, mitotic inhibitors, corticosteroids, etc. alone or in combination with together are utilized for cancer treatment. Despite the progress in oncology-related areas, lack of differentiation in targeting cancer and normal cells and achieving cancer therapies with minimum toxicity and high efficacy remains a big challenge, and ongoing therapeutic modalities almost are accompanied by huge unwanted side effects, whereas do not have appropriate performance [3]. Unfortunately, tumors gain resistance toward mentioned treatments during the treatment periods. In addition, conventional treatments have many unwanted side effects, whereas having no selective effect and target and kill cancer cells and their healthy counterparts [4,5]. The complex nature of cancer and the ineffectiveness of conventional therapies occasion major trouble for the healthcare system and emphasize the need to develop new therapeutic strategies [6]. Having a novel technology is of importance in many health challenges, and can be taken as a unifying element in science, bringing physical, engineering, and medical modalities together in times of trouble and in times of challenge.

Selective heating of electrons while heavy particles remain cold, distinguishes cold or non-thermal plasma from hot plasma in which electrons and ions have the same energy [7]. Gas plasma is produced by feeding gas, typically noble gaseous or combinational use of noble gaseous with O_2 and N_2 on one or several electrodes, in which electric field has guided between them. Reactive oxygen and nitrogen species along with electromagnetic field and UV radiation as the main output of gas plasma are produced in a controlled procedure depending on input parameters such as gas flow rate, external electric field, discharge voltage, target surface potential, quenching gas shielding, and target capacitance above ground [8]. Multimodal, adjustable, and cocktail of chemical and physical effects introduces gas plasma as an emerging and promising technology for a wide range of diseases e.g., wound healing, cancer treatment, inactivation of bacteria and viruses, food

industry, and surface modification [9–12]. Among medical applications, gas plasma oncotherapy has received great attention owing to its outstanding preclinical results. Based on chemical and physical factors, while eliminating resistance to chemotherapy and radiation therapy, can induce selective effects toward cancer and normal cells, especially at low to moderate doses, which is not achieved in conventional therapies [13, 14].

Here, we focus on the properties that make plasma an alternative and adjunctive therapy for cancer treatment. The strengths and weaknesses of used gas plasma modalities are presented. In addition, the molecular mechanism of this treatment comprehensive is discussed. Finally, by discussing the challenges in clinical translation, the prospective of gas plasma oncotherapy is presented.

2. Medical gas plasma: definition and applications

Gas plasma is a multi-state environment rich in reactive oxygen and nitrogen species (RONS), electric field, UV radiation, and low intensity of shock and heating waves, which is generated by applying electrical discharge to one or a set of electrodes that contains feeding gas [15]. Medical gas plasma, also known as cold or non-thermal plasma, is receiving extensive attention in the last decade due to its promising results in medicine. Various plasma devices have been explored and are present in the market, which contributes significantly to the industry and medicine. Plasma jet and dielectric barrier discharge (DBD) are two common types of plasma devices that are used in medicine depending on the biological target. While plasma jets are suitable for direct treatment due to their flexibility, DBD covers a larger surface area and can also be used for indirect treatment [16, 17].

The controllable and adjustable concentration of RONS, UV radiation, and EM fields leading to diverse applications for gas plasma in medicine including cancer therapy, wound healing, antibacterial effect, antiviral effect, and dentistry [18–20]. Despite the great advances in the application of gas plasma for wound healing and blood coagulation, so that this technology is now used as an adjunct therapy in clinics for wound healing and blood clotting, plasma cancer therapy is still studied at preclinical levels. Albeit numerous studies were conducted in the plasma cancer therapy areas, typically in-vitro and in-vivo studies, the lack of translational research in oncology is serious [17–21].

3. Gas plasma for cancer treatment

Gas plasma showed its advantage with multimodal nature in comparison to other physical oncotherapy modalities such as electrochemotherapy (ECT), radiotherapy (RT) photodynamic therapy (PDT), hyperthermia (HT), high hydrostatic pressure (HHP), and considered as novel technology which has significant implications in cancer treatment [22].

During the plasma treatment, some main factors influence the impact and efficiency of plasma such as device parameters, process parameters, and materials and procedures that are utilized for ex-vivo and in-vivo experiments. Treatment area, flow rate, working gas, gas composition, and shielding for tuning have been proposed as the basic parameters of the device that affecting the plasma output parameters [23]. Process parameters are the next indicator in the plasma exposure e.g., treatment time, incubation time, direct vs indirect, distance to effluent, and throughput can influence significantly the UV-VIS emission, positive ions, electrons, RONS, and microwave emissions. Further to the device and process parameters, cell type, morphology and physiology, surface receptor expression, volume and content of liquids, and chemical composition of liquids are essential effectors in the plasma treatment process. Surface integrity, treatment size, chemical composition of environment, and penetration depth are other indicators that should be considered for in-vivo experiments [8–24].

Given the outstanding primary features i.e., flexibility in use, dose-dependent effect, multimodality nature, mild effect, and redox flux increase to cells, gas plasma leading to promising outcomes in preclinical studies [13]. Accordingly, wide cancer types have been examined using gas plasma therapy, typically by employing self-made devices, resulting in cancer cells death and inhibiting tumor growth in the in-vivo model. It is noteworthy that despite the various mentioned factors influencing the plasma therapy process, plasma has been able to kill most of the investigated tumors, which introduces plasma as a novel technology for cancer treatment [25, 26]. Due to the ability to selectivity for cancer cells, stimulation of the immune system, enhancing cancer chemosensitivity, elimination of cancer stem cells, and halting cancer metastasis, plasma-based cancer treatment in comparison with conventional treatments, are considered as a highly emerging technology that has the potential to treat a variety of cancers in the years ahead [13–15].

The common denominator of in-vivo studies is the significant inhibition of tumor growth. Complete cessation of tumor growth was observed on the rat melanoma model after three weeks of plasma treatment. Although the mechanism of action remains a debate, activation of the immune system to attack the tumor and enhance macrophage function, which leads to increased antitumor function, is thought to be one possibility [27, 28]. In particular, the mechanism has been attributed to the H_2O_2 and NO_2^- and physical factors, which are produced from plasma or its interaction with air, liquid, or cells and tissues [29, 30]. However, the need to design and conduct further studies in this area and determine the exact role of physical and chemical factors is essential.

While the antitumor effect of gas plasma has been studied on melanoma, glioblastoma, lung cancer, colorectal cancer, head and neck cancer, pancreatic cancer, breast cancer, leukemia, thyroid cancer, and ovarian cancer in the animal phase, colorectal cancer, and head and neck cancer are the only clinical cases that have been studied through plasma therapy [31, 32]. Besides the independent use of gas plasma, it might be com-

bined with conventional therapies, where plasma can improve the efficacy of chemotherapy and radiotherapy and acts as a complementary approach for their selective performance and effectiveness. Carboplatin, paclitaxel, gemcitabine, temozolomide are several chemotherapy drugs that are studied in combinational use with plasma. It has been reported that plasma could re-sensitize chemo-resistant cancer cells to oncotherapeutic agents and increase their efficiency through the adjustable concentration of RONS and probably physical effect [29, 33–36].

Due to having a mild dose of electromagnetic field and RONS, gas plasma is proposed as a multimodal treatment that can be used simultaneously with other drugs such as chemotherapy, which in most cases leads to synergy. Low to moderate plasma doses inducing apoptosis, whereas high doses are accompanied by inducing necrosis in cancer cells [37, 38]. A cocktail of physical and chemical factors that is rarely available in conventional cancer treatments, makes plasma a cost-effective and effective method that can be combined with conventional therapies for a wide range of cancers without damaging healthy cells, at least in the preclinical phase [39, 40]. Furthermore, gas plasma can be utilized for a range of cancer patients without effective treatment, radiation-resistant, cancers with physical isolation, and patients with metastases, cancers that require low penetration depth, and even for patients after surgery [13]. The main components and dose-dependent cell deaths of gas plasma are documented in Figure. 1 and comprehensively are presented in the next sections.

4. Gas plasma dose in oncology

One of the most important milestones in plasma medicine is the definition of plasma dose. Although the exact plasma dose has not yet been determined, a collection of generated RONS, UV radiation, EM field, which are dependent on the liquid surface area, treatment time, cell amount, thickness of medium or solution, distance from nozzle, discharge voltage and frequency, type and rate of gas flow, can be considered as plasma dose [38–41].

For instance, the concentration of RONS increases with raising input discharge voltage. Also, as the distance from the nozzle increases, the RONS concentration decreases. The lower solution volume exposed to plasma leading to the greater production of RONS concentrations [42]. Most importantly, the increasing treatment time will be associated with the enhanced RONS production. Accordingly, plasma dose is defined as a flexible and adjustable component dependent on input and process parameters and is one of the key factors in achieving the desired biological responses [43]. Overall, by ignoring the physical effect, the dose of plasma can be defined depending on the concentration of RONS produced in three groups: low, medium, and high, which each of them is accompanied by specific biological responses.

5. Treatment methods

Plasma treatment is applied to the biological target in direct and indirect forms. In direct treatment, tumor cells and tissues are exposed to direct plasma radiation in preclinical studies and patients in clinical trials. While in indirect treatment, tissue and cells are basically not exposed to direct plasma radiation. In this section, we will briefly describe each of these methods and discuss their applications.

5.1 Direct treatment

In the direct treatment of physical agents of electric field and UV radiation along with RONS in plasma therapy process play a major role, so that the generated cocktail of these chemical and physical effects generated in interaction of plasma plume with air, liquid, and cells and transferred to the target. Compared to the indirect treatment, synergies between chemical and physical effects in this approach brings about a great environment for cancer treatment. Albeit this procedure is suitable for surface targets, due to the limited penetration depth of RONS, direct plasma treatment faces some troubles for tumors in-depth tissue [8–44].

5.2 Plasma treated solution

Indirect plasma treatment is gaining attention due to desirable features and developed during the last years to facing with direct treatment challenges. In this method, the solution is exposed to plasma irradiation and the treated solution is added to the desired biological target. In contrast to direct treatment, where plasma treatment consists of physical and chemical factors concomitantly, in indirect treatment, plasma generated RONS play a major role and the effect of physical agents is negligible [45, 46].

The existence of various additives in the culture medium might change our outcomes owing to the interaction between solution compositions and plasma-produced RONS. Hence, in the perspective of PTS, solutions that have a minimum reaction with RONS, UV radiation, and EM field should be used. In addition to different culture mediums, various solutions including water, PBS, Ringer's lactate solution (RL), etc. have been used as solution resources for plasma treatment. Interestingly, apart from the type of solution, PTS can induce anti-tumor effects, especially for intraperitoneal cancers [47, 48].

5.3 Plasma-assisted immunotherapy

In addition to plasma-treated solutions, plasma-assisted immunotherapy, which aims to use plasma as a modulator of the immune system, recently explored indirect plasma treatment that can be revolutionized oncology research. As a major cause of immunogenic cell death (ICD), plasma-produced ROS can be reported to stimulate macrophages and increase cell death, a process associated with alpha tumor necrosis factor released from plasma-activated macrophages [49–51]. It seems that in addition to the use of plasma as adjunctive therapy with conventional drugs, a combination of indirect

and direct plasma therapy can be used to cover the challenges facing cancer therapy in the future.

6. Selectivity mechanism of gas plasma toward cancer and normal cells

Compared to the conventional onco-therapeutic modalities, gas plasma can induce selective impact on normal and cancer cells, so that cancer cell dies, but their normal counterparts significantly remain unaffected [53]. This section focuses on the mechanism of this selective effect. From the point of view of the action mechanism, gas plasma can perform selective actions by taking advantage of the structural differences between cancer and healthy cells, i.e., differences in basal redox of cancer and healthy cells, differences in cholesterol, and aquaporin concentrations in cancer and healthy cells.

Regarding basal redox in healthy and cancer cells, healthy cells have lower baseline RONS levels than cancer cells, which makes them more capable of increasing external RONS [54, 55]. As plasma-generated RONS increases, the RONS level of cancer cells reaches the threshold level, and as a result, the process of cell death begins through a variety of pathways [56, 57].

On the other hand, the high cholesterol on the membrane of healthy cells makes them more resistant to the increase in RONS, while the concentration of cholesterol on the surface of cancer cells is much lower and consequently on the increase of RONS are vulnerable [58,59]. In addition, cancer cells have higher concentrations of aquaporin compared to healthy cells, thereby high concentrations of aquaporin are the infiltration of more RONS, especially H_2O_2, into the cell [60–62]. Thus, a set of factors related to the structural differences between cancer and healthy cells, along with the unique environment of plasma leads to selectively function toward cancer cells versus their healthy counterparts.

Despite the different expression of aquaporin and cholesterol in healthy and cancer cells, H_2O_2 cannot be considered as the only selective factor in plasma, because healthy cells are far more sensitive to H_2O_2 [56, 63, 64, 64]. In fact, cancer cells have a specific expression of NOX1, catalase and SOD at their surface, whereas healthy cells lack this expression [52, 65]. In general, plasma-derived RONS, especially H_2O_2 and NO_2^-, stimulate the selective process by producing primary O_2^-, which inactivates catalase, and thus begin the process. In the next phase of the H_2O_2 and $ONOO^-$ interactions produced by tumor cells that can survive longer by catalase inactivation, secondary single oxygen is produced and thus, in addition to further catalase inactivation, HOCl signaling is activated. It is at this point that H_2O_2 enters the cancer cells to induce apoptosis through aquaporins, resulting in reduced glutathione [56, 65, 66].

7. Molecular mechanisms of gas plasma oncotherapy

The apoptosis pathway contains a variety of proapoptotic and antiapoptotic proteins. Whenever proapoptotic proteins expression are reduced or antiapoptotic proteins expressions are increased, the apoptotic pathway is inhibited, thereby intrinsic resistance to common treatments have occurred. To combat this resistance, inducing apoptosis should be considered in alternative treatment efficacies. Inducing apoptosis, intrinsic and extrinsic pathways, in tumor cells indicating the efficacy of antitumor effects of used therapeutic agents. Overexpression of proapoptotic proteins and under-expression of antiapoptotic proteins represents apoptosis induces in cells. As discussed, apoptosis is the main mechanism at low to moderate doses, and most studies emphasize the occurrence of plasma-induced apoptosis [38]. In some studies, that have reported necrosis, high plasma doses have been used [67]. Involvement in the cell cycle is a strategy for targeting cancer cells, because cancer cells grow faster than normal cells. In this regard, the effect of plasma on cell cycle has been extensively evaluated. The findings indicate that due to the presence of more cancer cells in the S phase, their vulnerability to plasma therapy is higher than healthy cells [68].Furthermore, it is currently believed that in most cases, DNA damage caused by plasma therapy [69]. Mitochondrial apoptosis is the prevalent biological response under plasma treatment, and in most cases, this response is to plasma-derived RONS leading to DNA damage [70, 71]. Besides the intrinsic apoptosis pathway, the extrinsic apoptosis pathway has also been reported in some cases [72]. In addition, G2/M cell cycle arrest as a result of plasma treatment has been observed for several cancer cell lines without addressing the relevant mechanism [73].

Another feature of gas plasma in the treatment of cancer is the ability to stop metastasis, where plasma with EMT inhibition has been proposed as a new way to inhibit metastasis [74]. In addition, plasma has been shown to be able to inhibit metastasis by reducing the expression of several relevant genes.

8. Conclusion and future considerations

One of the most important challenges in cancer treatment is the lack of targeted and selective treatment approaches. Also, cancer cells become resistant to the common treatment over time, consequently, the effectiveness of common treatments, especially chemotherapy and radiation therapy, decreases. Despite increasing studies in understanding the molecular mechanism of cancers, some aggressive cancers remain unknown. Designing clinical randomized trials would be predicted for some cancer types, such as skin cancer, whereas in other aggressive cancers like anaplastic thyroid cancer, preclinical studies are proposed due to inadequate knowledge in cancer nature.

Gas plasma cancer therapy is gaining great attention as a new strategy for cancer treatment owing to the multimodal, mild and adjustable dose, and ability to combine with conventional

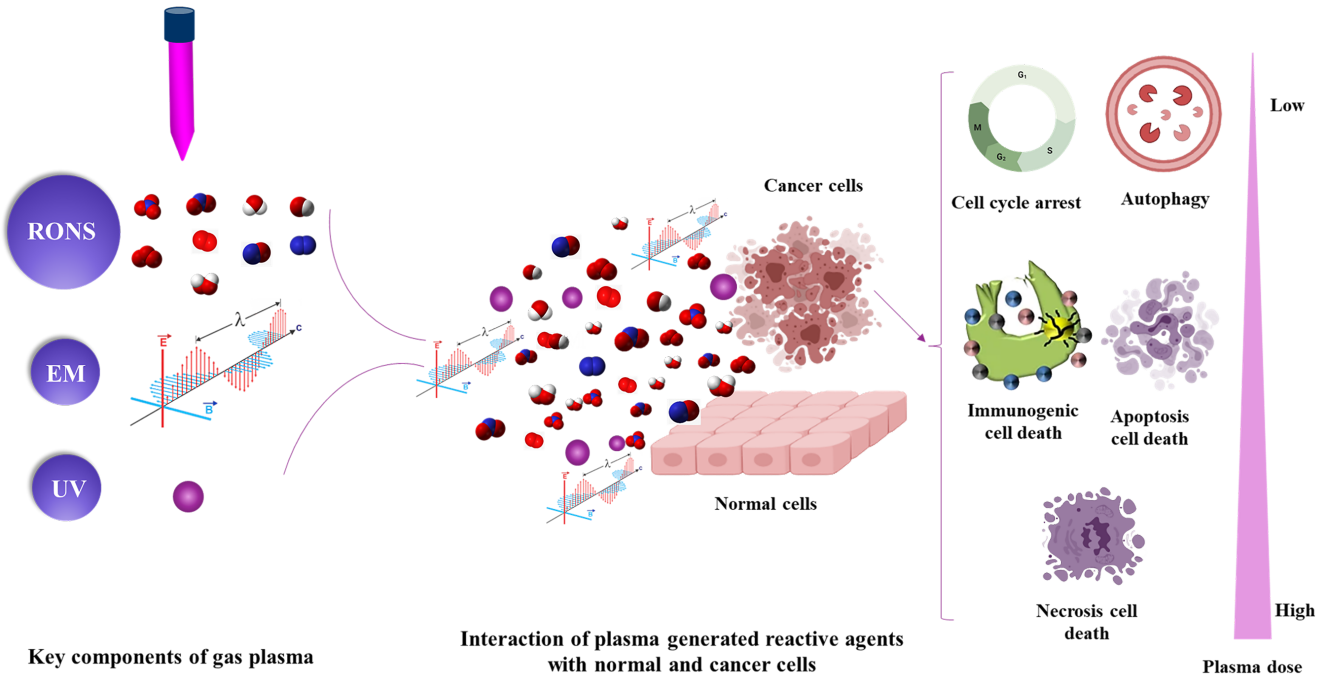

Figure 1. Reactive agents from generation in plasma to inducing selectively dose-dependent cell deaths.

therapies properties. Plasma treatment is used directly and indirectly to address the major challenges of cancer therapy. While conventional therapies fail to induce selective function, gas plasma targets cancer cells quite selectively, using structural differences between cancer cells and healthy cells, and exerts this function in several stages. Depending on the plasma dose, apoptosis, macrophage and necrosis occur. Although very promising results have been obtained in preclinical studies, the design of clinical trials for this technology is in its infancy. Plasma devices standardization and precise molecular mechanisms must be designed before transfer to clinical practice.

The breadth of studies in vitro and the variability of the factors involved in each study is such that the overall conclusion about the plasma dose and the exact influencing factors is difficult because, in addition to the different plasma jets used, where the input parameters and the configuration of each device can affect the results, the treatment process and the factors involved in the biological arrangement of the experiment are also very different. For example, the types of culture media used to produce plasma-treated solutions make it impossible to draw a general conclusion about this, because with each culture medium and solution studied, the minimum concentration of RONS species produced can be changed. The most influential factor in the plasma therapy process varies, and a single protocol for the plasma-treated solution cannot be achieved, at least during this time. In this regard, the concentration of H_2O_2, NO_2^- and NO_3^- as the main RONS in the plasma treatment process, by changing the input parameters, experimental design, and the solution types are so different that it can affect the experimental outcomes. All of the above indicate the complexity of plasma chemistry, and more detailed studies should be performed under the same conditions. Notwithstanding great progress in the preclinical phase, especially in the field of the mechanism of action and stimulation of the immune system, clinical studies have been rarely conducted and more attention has been paid to designing clinical studies that the plasma pathway to the clinic and the introduction of plasma as a complementary or independent cancer treatment that can be a substitute for conventional treatment is essential. As noted, there are several barriers to the transfer of gas plasma to clinical applications, including access to deep tissues, which is currently thought to be solvable using the plasma-treated solution or plasma-assisted immunotherapy. However, there are widespread plasma solutions interactions, which have unpredictable consequences with current plasma oncology.

While for superficial tumors, the translation possibility can be predicted to be far greater than in-depth tumors, standardization of devices and diversity of devices and their self-fabrication are also considered challenges in this area. In the meantime, stimulating the immune system with plasma can raise hopes, but the focus of plasma oncology should be on developing standard devices with modern and optimal needs, which can be used in clinical applications. Although plasma devices have a variety of functions as discussed throughout, it is essential to design and build an anti-tumor plasma device for translation to the clinic. In addition, defining plasma doses remains a challenge, both theoretically and empirically. It is hoped that in the future, some research groups will focus on this issue, examining plasma dose as a factor dependent on input factors and the plasma therapy process.

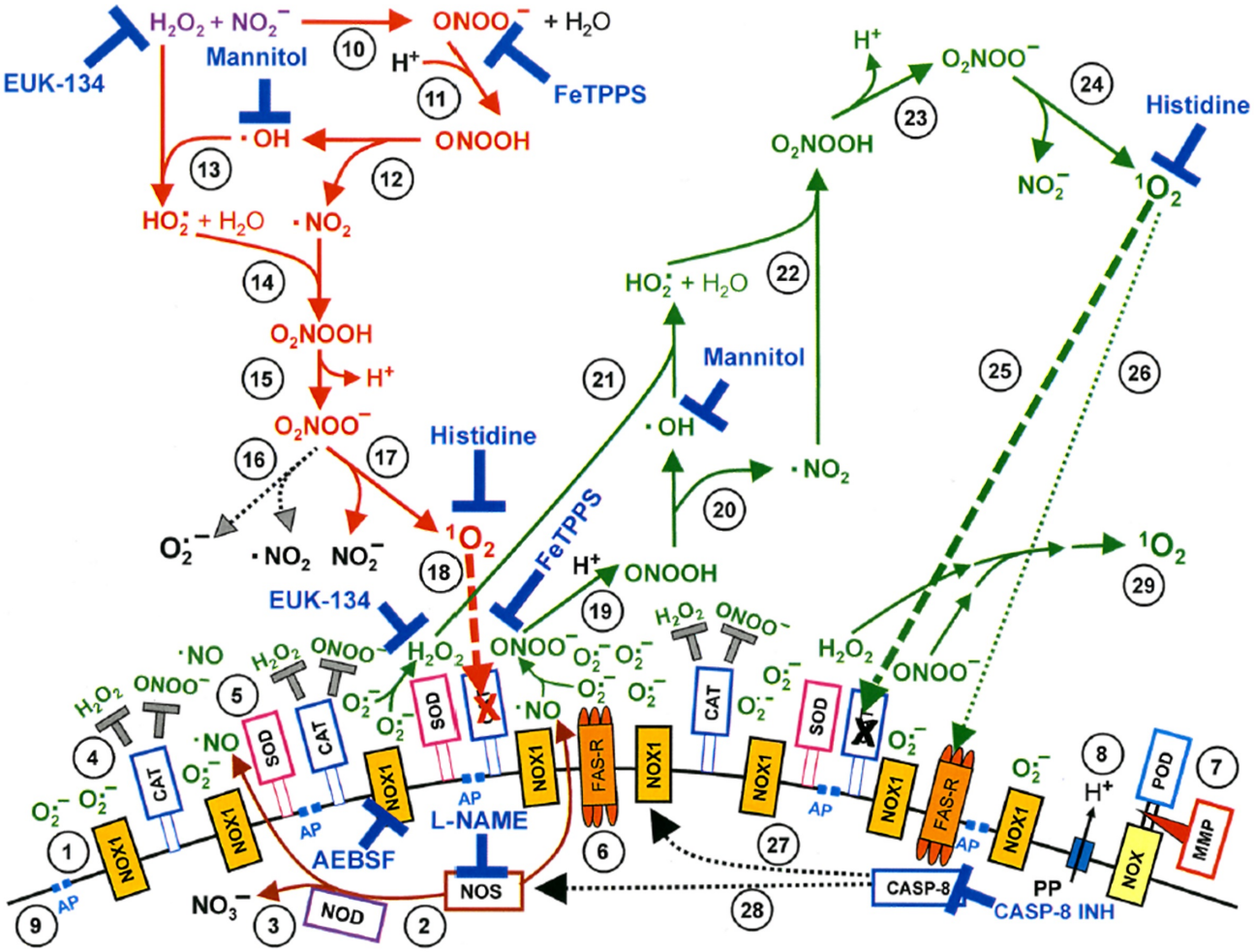

Figure 2. Apoptosis induction by gas plasma is mediated by the generation of primary and secondary singlet oxygen ($^1O_2$). NADPH oxidase 1 (NOX1) is expressed in the membrane of tumor cells and generates extracellular superoxide anions ($O_2^{\bullet -}$)(#1). NO synthase (NOS) (#2) generates $^{\bullet}NO$ 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 references, on singlet oxygen generation in references, and on intercellular apoptosis-inducing signaling after catalase inactivation in references. This figure was obtained with permission from [52] under the terms of Creative Commons CC BY license.

In order to create coordination between research groups and help the rapid growth of this field, a clear framework for the standardization of devices should be provided so that the overall results of plasma cancer treatment outcomes can be deduced from the results of studies. Another important point is the careful study of the mechanism of action, which should be focused on in the coming years in order to introduce plasma as an alternative or adjunct to cancer therapy to the medical community.

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The authors declare that they have no conflict of interest.

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