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Gas Plasma for Medical Applications: Wound Healing and Oncotherapy

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ABSTRACT

Cancer and wound healing leading to high mortality and healthcare problems. To provide therapeutic insights into oncotherapy and wound healing challenges, there is an urgent need for novel technologies. The use of physical plasma for medical purposes is known as medical plasma and this field consists of plasma physics, biochemistry, biology, and medicine. Plasma medicine is one of the most innovative and emerging areas and provides a promising strategy for a variety of diseases including wound healing, cancer therapy, biofilm removal, virus inactivation, dentistry and ophthalmology. The discovery of the multimodal nature of gas plasma (GP) for widespread medical applications revealed that its efficacy is related to the reactive oxygen and nitrogen species, electric field, and UV radiation. The combination of these agents brings about a unique platform for medicine. Here, along with summarizing the nature of GP, wound healing, and cancer, we review some of the latest work regarding the application of GP for oncotherapy and wound healing.

Keywords: Gas plasma, Plasma medicine, Oncotherapy, Wound healing

INTRODUCTION

Despite significant advances in medicine, especially medical equipment technology, medicine in the 21st century faces significant and growing challenges [1]. The ever-increasing global population in general and the aging population in the world are increasing the need for health care worldwide [2]. Wound healing and cancer treatment as two major health system challenges that endanger the lives of millions of people every year [3-5].

In spite of significant efforts to develop novel strategies and various therapeutic products, clinical success in the treatment of chronic wounds has been limited mainly due to the complex nature of the wound healing process and limited understanding of the mechanical, biochemical, immunological and biological repair processes involved [6-8]. However, disorders of the wound environment rich in degrading enzymes and its increase in pH, along with differences in the time scale of different physiological processes involved in tissue regeneration, require the use of effective drug delivery systems and multistage strategies. An ideal wound strategy should treat wounds at a reasonable cost and with the least hassle for the patient [9,10].

Cancer is a global concern and leading to high mortality and morbidity rates. The current situation of oncotherapy has created a major problem for the health system. Surgery, chemotherapy, radiotherapy and a combination of them are the current traditional treatment for various cancers. Due to the limited therapeutic efficacy of conventional modalities, the majority of efforts in oncotherapy studies focus on new therapeutic strategy achievement [11-13]. Despite the recent advancement of oncotherapy research, minimizing toxicity for anti-cancer therapies while getting maximal therapeutic benefit remains a big challenge. Therefore, to improve the efficacy of the current oncotherapeutic agents, there is an urgent need for a multimodal anticancer strategy [14,15].

Plasma medicine is the use of physical plasma for medical applications and combines plasma physics, chemistry, biochemistry, cell biology and medicine. It has emerged as a new solution to address medical problems [16,17]. In recent years, plasma medicine has achieved

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many early and promising successes in widespread areas. One of the unique features of cold atmospheric pressure plasma, also known as gas plasma (GP), is its low gas temperature. GP, in which the temperature of the ions is close to room temperature, is produced by applying a noble gas to a paired electrode connected to kV sine waves pulses or in radiofrequency [17-20]. Oncotherapy and wound healing are two applications in which GP has appeared very promising. Clinical studies have been conducted in both areas and the results obtained so far have been very impressive [21,22]. In this review, we first list the challenges facing cancer treatment and wound healing, and then review studies in this area using plasma technology.

GAS PLASMA

Plasma is divided into three types, hot, warm, and non-thermal [23]. GP also known as cold plasma receives its reaction through high-energy electrons, while ions and neutral species remain cold. In GP, the composition and temperature can be adjusted in a wide range with parameters such as input energy type, input power, type, flow, and gas composition [17,24]. In most cases, GP is produced using an electric field in a noble gas, air, or mixture of noble gas with O_2 or N_2 gas mixture, respectively [25,26].

GP represents ionized gases with ion temperatures close to room temperature. The composition of GP is very complex and consists of ions, charged particles, electrons, electric fields, free radicals, small amounts of ultraviolet light, and neutral molecules. Although, emerging evidence suggests that, among other components, reactive oxygen species (ROS) and reactive nitrogen species (RNS) act as major mediators of biological responses to GP treatment, but physical factors such as UV and electric field have also crucial roles (Fig. 1) [17,27-29].

In fact, ROS and RNS are well known for regulating and influencing major cellular processes, such as cell growth, migration, proliferation, differentiation, death, inflammation and regeneration [27,30]. Various studies have repeatedly shown that GP is capable of producing several RONS such as H_2O_2, NO_3^-, NO_2^-, O, ^-OH, O_2^-, $^1O_2$, NO^-, or O_3. Therefore, it is not surprising that GP has different biological effects. It is worth noting here that the intracellular actions of ROS and RNS also include promoting or suppressing inflammation, immunity, and carcinogenesis [31-34].

WOUND HEALING

Delay wound healing affects millions of people around the world through high mortality rates and associated costs. Lack of a suitable environment to facilitate cell migration, proliferation and angiogenesis, bacterial infection and long-term inflammation are the three main problems of chronic wounds [35-38]. The current approach to managing chronic wounds involves debridement, the use of different types of dressings such as hydrocolloids and hydrogels, or the use of negative pressure wound therapy [39,40]. In more serious wounds, it is necessary to use advanced therapies such as bioengineer skin replacement or growth factors, and finally autologous skin grafts. Despite many modalities and agents developed to accelerate the wound healing process, wound treatment still does not bring acceptable results [41]. Wound debridement is associated with complications such as bleeding, pain, or infection. Topical delivery of therapeutic drugs such as antibiotics or growth factors is limited due to the catabolic wound environment as well as the presence of biofilms [42,43]. On the other hand, current wound dressings are not optimal due to limitations including insufficient mechanical properties, poor adhesion, and traction. These defects require the use of secondary dressings, which in turn increases the risk of additional infection or trauma and complicates the treatment process [44]. In addition, most existing products are designed to be one-activity and eliminate only one set of disrupted processes, which completely hinders their overall success in healing chronic wounds. Therefore, current therapeutic approaches have not been able to overcome wound healing challenges and leading to limited clinical success [35,45,46].

The multimodal nature of plasma, as illustrated in Fig. 2, is such that by combining all the factors involved in the plasma healing process, a set of critical wound healing responses, such as sterilization, increase in provides microcirculation and acidification of the skin, *etc*., and makes a the noticeable distinction between itself and other common methods [47,48].

Among the advantages of using plasma compared to

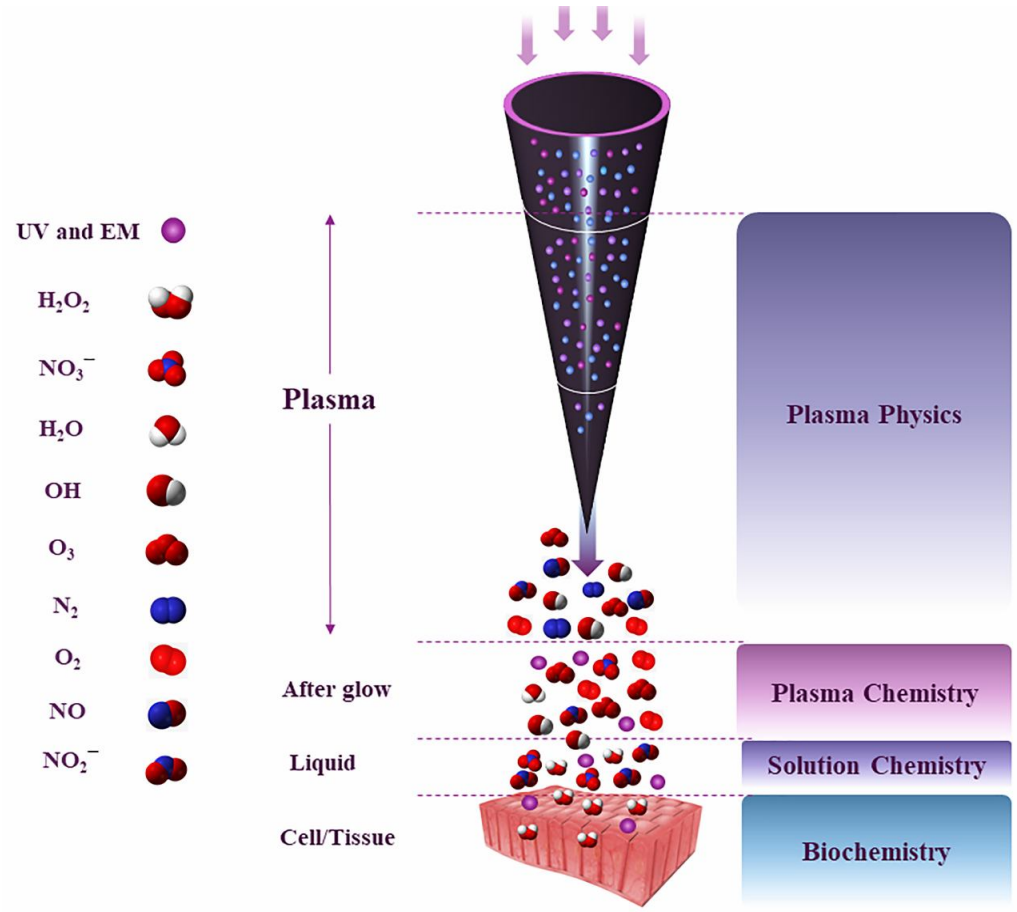

Fig. 1. Chemical and physical factors of plasma from generation and transport to interactions with biological objects.

other common methods can be a further reduction of bacterial load in preoperative conditions, reduction of postoperative pain level, shortening the recovery period wounds. Preliminary research has been done to understand the effect of plasma on the molecular level of the cell, and the results suggest that plasma can produce a biological change related to proteins, DNA, and amino acids. It can also stimulate cell proliferation or death and improve cell function [49,50].

Due to advances in engineering and materials sciences in parallel with chemistry and biomedical sciences, the economics and safety of GP resources are constantly increasing. Advances in experimental and numerical diagnosis in the interaction between GP and biological objects are a key theoretical basis for further development of plasma medicine. The use of GP for the skin is now increasingly recognized as one of the most widely used applications in plasma medicine, and many results have already been performed in clinical applications such as chronic wounds and the treatment of common skin diseases. Ongoing studies have raised hopes that GP may eventually emerge as a critical factor in the treatment of diabetic foot ulcers and skin diseases such as melanoma and psoriasis [51-53].

Resistance and allergic potential in patients to antibiotics are the crucial weakness of systemic antibiotic treatment. By combining effective eradication of multiple resistant microbes and lack of resistance in microorganisms to it, GP therapy creates a new platform for wound healing management and these advantages are related to the

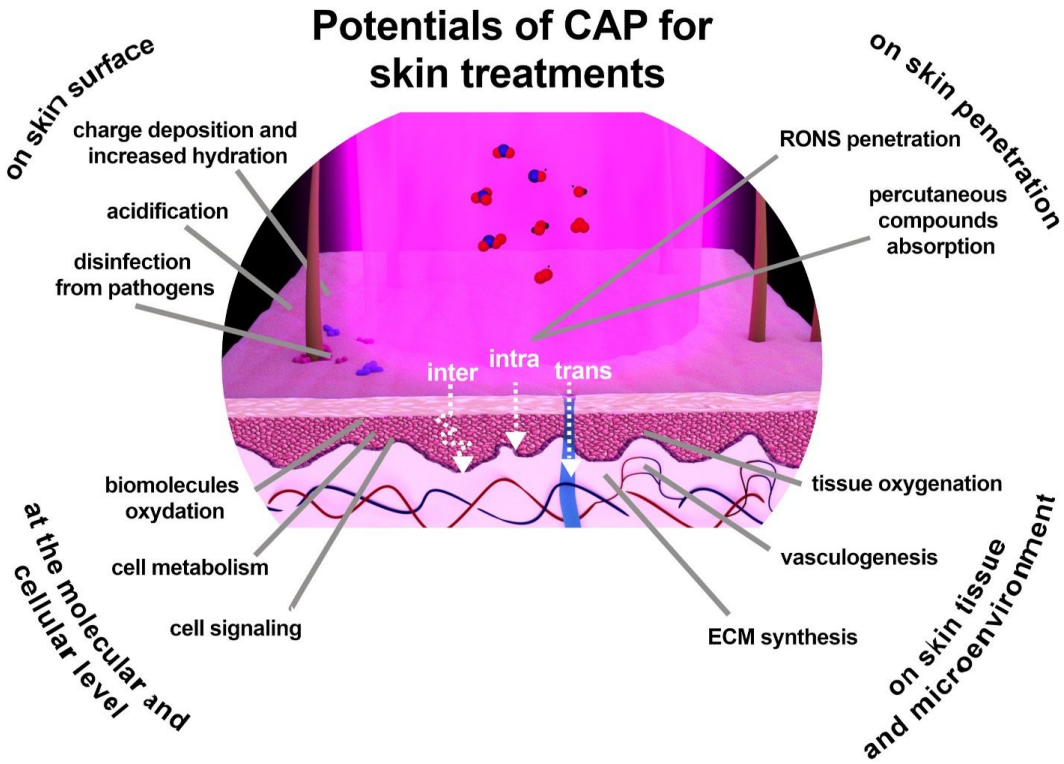

Fig. 2. Potentials of CAP in skin biology. CAP performs its activity at various levels of the skin. At a superficial level, it promotes the hydration, acidification, and decontamination of the stratum corneum. CAP-generated RONS can penetrate inside the skin *via* the intercellular way (inter), the intracellular way (intra), or *via* the transappendageal way (*trans*). By loosening the cutaneous barrier, CAP also promotes the absorption of other molecules such as drugs. At a molecular level, once penetrated the skin, RONS can have a direct effect on skin biomolecule oxidation or activate cell metabolism and signaling. At the tissue level, CAP treatment leads to an increase in skin oxygenation, stimulates vasculogenesis, and the ECM remodeling or de-novo synthesis. Abbreviation: CAP, cold atmospheric plasma. This figure was obtained with permission from [47] under the terms of the creative commons CC BY license.

physicochemical properties of the plasma. On the other hand, non-invasive, painless use, as well as their gaseous state, which allows them to penetrate the smallest areas, such as the marginal area of fistulated wounds are another advantage of GP therapy in comparison to common strategies [47,54]. In addition, plasma reduces the pH levels, which is important for accelerating wound healing. GP has been shown to enhance endothelial cell proliferation even by stimulating angiogenesis through the release of growth factors. It is well known that the body responds naturally by wound acidification due to skin damage. Also, the pH value in the environment of chronic wounds affects various factors of wound healing [47,55,56].

A recent in vitro and in vivo study was conducted to evaluate the effect of GP as a treatment for diabetic wounds. Eight-week-old male db/db mice and C57BL mice were treated with GP for 90 s and 180 seconds for 2 weeks with helium gas plasma. Blood and skin samples were collected from around the wound. After 14 days of treatment, GP healed diabetic wounds and the wound closure rate was significantly higher than the control group. IL-6, tumor necrosis factor-α, nitric oxide synthase and superoxide dismutase protein expression were significantly reduced in the GP group compared with the control group. However,

vascular endothelial growth factor and growth factor-expressing protein groups were significantly increased in the two GP-treated groups. Besides, there was no difference in normal skin histological observations, nor was there any difference in the levels of alanine transaminase, aspartate aminotransferase, blood urea nitrogen, creatinine and white blood cells among GP and controls. Hence, 3 min of GP treatment daily showed that overcoming inflammation, reducing oxidative stress and increasing angiogenesis, involving different protein signals with GP treatment, wound healing in diabetic rats, and GP treatment was safe for liver and kidney [57].

Another interesting study examined the potential use of plasma in dog bite wounds. In this study, the effect of GP was analyzed on the following bacterial strains commonly found in dog saliva: *Staphylococcus pseudintermedius*, *Staphylococcus aureus*, *Streptococcus concise*, *Pseudomonas aeruginosa*, *Pasteurella multocida*, and *Escherichia coli*. GP exerted an in vitro antiproliferative effect on all of these bacteria. The result showed that the use of GP in the treatment of dog bite wounds will be useful [58].

However, the current potential for GP use in these acute wounds can be expected to increase, especially as the increasing resistance of these bacterial strains complicates treatment. The results of animal studies and clinical trials showed that NO-containing gas plasma was associated with tissue disinfection and regulation of inflammatory processes associated with acute and chronic wounds and respiratory problems [59].

Numerous studies have described the lethal effects of GP on microorganisms such as bacteria and fungi and have shown its potential as an effective disinfection device. Fungal infections of the skin and nails, chronic wounds, and multidrug-resistant pathogens such as *S. aureus* (MRSA) are important medical and economic problems. Therefore, new treatments for this condition are essential. The challenge of increasing global microbial resistance, including a variety of pathogens including methicillin-resistant MRSA, vancomycin-resistant *enterococci*, and gram-negative species producing beta-lactam hydrolysis enzymes (β-lactamases), needs to be treated Creates alternative antimicrobials. In addition to the above features, GP treatment has a different mechanism of action compared to traditional antimicrobials and may act as an alternative to conventional antibiotic and antiseptic treatments [60].

To understand the effects of GP on mammalian cells, an argon-based GP jet was used to treat L929 mouse fibroblasts as well as BALB/c skin lesions. This study showed that when fibroblasts were treated with GP for 15 s, there was a significant increase in cell proliferation, epidermal growth factor and β-growth factor secretion, intracellular ROS production, and the percentage of cells in the S phase. Phosphorylated p65 protein and cyclin D1 showed a decrease in kappa B inhibitor protein expression. *In vitro* study showed that exposure to GP for 30 s increased the number of fibroblasts and the ability to synthesize collagen, while exposure to 50 s resulted in the opposite result. This result suggests that GP induces wound-healing fibroblast proliferation by inducing ROS production, overexpressing phosphorylated p65 expression, reducing inhibitory kappa B expression regulation, and activating the NF-κB signaling pathway, leading to a reversal of the process [61].

Schmidt *et al.* Showed that the p53 cascade should be a major center of GP cell-cell interactions in keratinocytes [62]. Also, MRC5 fibroblast cell lines and HaCaT keratinocyte cell lines proliferated examined after short-term GP exposure. The effect of plasma on *in vivo* studies in rat models showed that the wound healing observed was due to the formation and function of NO, UV and RONS [63]. For more detail about the gas plasma effects in wound healing refer to [64] (Fig. 3).

ONCOTHERAPY

Cancer therapies currently have the lowest clinical success rates compared to other diseases. As the current trend continues, resulting in a shortage of successful anticancer drugs, the disease will soon become a major challenge to governments' health systems. Combining existing approaches with new technologies can resolve this challenging problem [12,14]. Here, we provide an overview of the recent work regarding the application of GP for oncotherapy.

In the field of oncology, GP has attracted a great deal of attention because it is able to induce cell apoptosis in cancer cells [65]. It also shows selectivity towards cancer cells

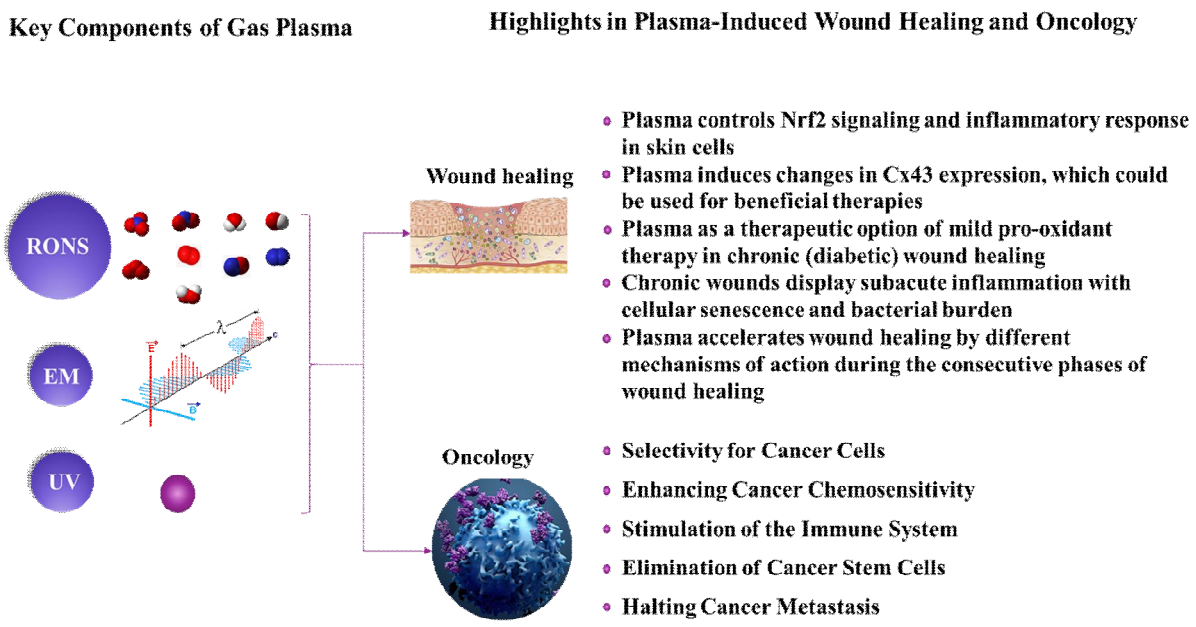

Fig. 3. The main physical and chemical factors of plasma and its highlighted effects in wound healing and oncology.

without damaging the surrounding tissue [66]. GP has been used to treat various tumor types. Currently, the remarkable anti-cancer capability of GP has been demonstrated by dozens of *in vivo* and *ex vivo* experiments with various cancer cells including liver cancer cells, lung cancer cells, glioma cells, skin cancer,

GP has been shown to be an excellent choice in killing cancer cells while not damaging normal healthy cells [21]. All of the discoveries for the application of GP in oncology documented in Fig. 3. For more information on this topic, refer to [21] references. One of the hypotheses explaining this choice is that cancer cells show a much higher rate of metabolism than normal cells and are therefore under high oxidative stress [69].

GP was also studied for the treatment of neuroblastoma *in vitro* and a mouse model. Cultured neuroblastoma of mice was exposed to GP for 0, 30, 60 and 120 s and then their apoptotic and metabolic activity was assessed immediately after treatment as well as 24 h and 48 h later. Tumors 5 mm in diameter were treated with GP. Then, tumor volume and rat survival were determined. Plasma therapy, in proportion to the time of exposure and after treatment, reduces metabolic activity, induced apoptosis, and cancer cell survival. *In vivo*, the tumors also underwent a single treatment, which ultimately reduced tumor growth. In addition, survival almost doubled [70].

MCF-7 breast cancer cells were also analyzed. Preliminary results showed that cell viability decreased after GP treatment due to increased apoptosis. Ninomiya *et al.* then showed that GP causes damage to 50% of breast cancer cell lines, regardless of whether they are MB-231 cell lines or MCF-7 non-invasive cell lines. Finally, anti-proliferative effects of GP were also observed in cell lines induced by human breast cell metastases [71].

By evaluating the effect of plasma depletion on T98G, A549, HEK293 and MRC5 cells, Kaushik *et al*. showed the effects of ROS on tumor cell death. The results showed that the viability of non-malignant HEK293 and MRC5 cells was slightly affected compared to cancer cell lines. ROS and H_2O_2 produced by plasma irradiation altered the potential of the mitochondrial membrane, initiating this innate apoptotic pathway and leading to the increased overall expression of the apoptotic gene and decreased expression of the anti-apoptotic gene. There was also a change in the cellular signaling activity of ERK1/2/MAPK at the protein level [72].

Studies on cell lines and animal models have repeatedly demonstrated the benefits of GP devices and their antitumor activity. Previous work reported that after plasma therapy, glioblastoma cell lines lost their viability. The study also showed that cell lines previously resistant to a temozolomide alkylating agent became sensitive to it [73].

Kim and colleagues then studied the effect of *in vivo* GP on mouse models and the *in vitro* effect on melanoma B16-F10 cell lines. Cell line results were obtained at 48 hours after 3 min of GP treatment and *in vivo* tumor contraction was comparable to that obtained by chemotherapy. In summary, the analysis of the effects of GP in the treatment of skin tumors was performed for the first time because plasma is easily applied directly to the skin structures. For example, G361 melanoma cells had reduced survival after GP use and were isolated from the surface. These cells had lower integrin and FAK expression and altered the fibrous structure of actin. They suggested the possibility of linking the plasma-facilitated cell death to integrin-ECM interactions. It was also possible to increase the antiproliferative effect of GP on melanoma cell lines by using plasma with gold nanoparticles bound to anti-FAK antibodies [74].

In another study, the efficiency of a GP device in two head and neck cancer cell lines was investigated. The results showed that plasma significantly reduced cell viability at all treatment times (30, 60, 90, 120 and 180 s) and lead to induces of apoptosis in cancer cells. Dose-dependent DNA fragmentation is also a major factor in the anticancer effects of GP [75].

The antitumor activity of GP has also been tested *in vitro* in two human cancer cell lines (glioblastoma U87MG and colon cancer HCT-116). The results showed that GP produced large amounts of ROS and damaged DNA damage, which stopped the multi-phase cell cycle and induced apoptosis. In addition, *in vivo* experiments on rats xenograft from U87MG showed that GP reduced tumor volume. Induction of apoptosis, as well as accumulation of cells in the S phase of the cell cycle, was also considered, indicating that cessation of tumor proliferation has occurred [76].

Then, to determine the clinical application of GP in squamous cell carcinoma of the head and neck, 12 patients with advanced head and neck cancer and infected wounds used GP treatment and subsequent palliative treatment. Four of these patients responded at the tumor level after 2 weeks of treatment. Tumor surface reaction is associated with vascular stimulation or contraction of tumor wounds. In a similar case, 9 patients with the same type of cancer were treated with GP before the tumor was removed, and the samples collected from the tumors were evaluated for apoptotic cells. Apoptotic cells appeared mostly in GP-treated tissue areas [77].

Another clinical study evaluated the effects of GP treatment on six patients with advanced head and neck cancers. Two of these patients clearly responded positively to treatment by reducing tumor size. While the tumor in one of these patients begins to grow again and leads to the death of the patient. No side effects were observed in two patients, while four patients experienced fatigue and dry mouth. From the six patients at baseline, five died after 1 to 12 months, which was found to have nothing to do with GP treatment. The role of ROS/RNS, myeloid cells and the model of immunogenic cell death in cancer treatment as potential mechanisms for the performance of GP treatment was thoroughly discussed [78].

Rasouli *et al*. evaluated the mechanism of selective non-thermal plasma and two common chemotherapy drugs on A2780 CP and SKOV-3 as ovarian cancer cells and healthy GCs as ovarian normal cells. The findings indicate that plasma targets cisplatin-resistant cancer cells with high selectivity and breaks down the major barrier to the treatment of this cancer. In addition, the plasma-activated medium (PAM) exhibits a better selective effect than direct plasma irradiation. On the other hand, carboplatin, in doses used in clinical cases, has no significant effect on the survival of cancer cells and healthy. Also, paclitaxel, another anti-cancer drug, targets healthy cells more than cancer cells by exerting a negative selective effect and significantly reduces their survival. In general, PAM induces intrinsic apoptosis and in comparison to direct irradiation, carboplatin and paclitaxel has a suitable selective performance in ovarian cancer cells (Fig. 4) [79].

CONCLUSIONS

Non-thermal plasma has emerged over the years as a promising alternative for a range of medical challenges.

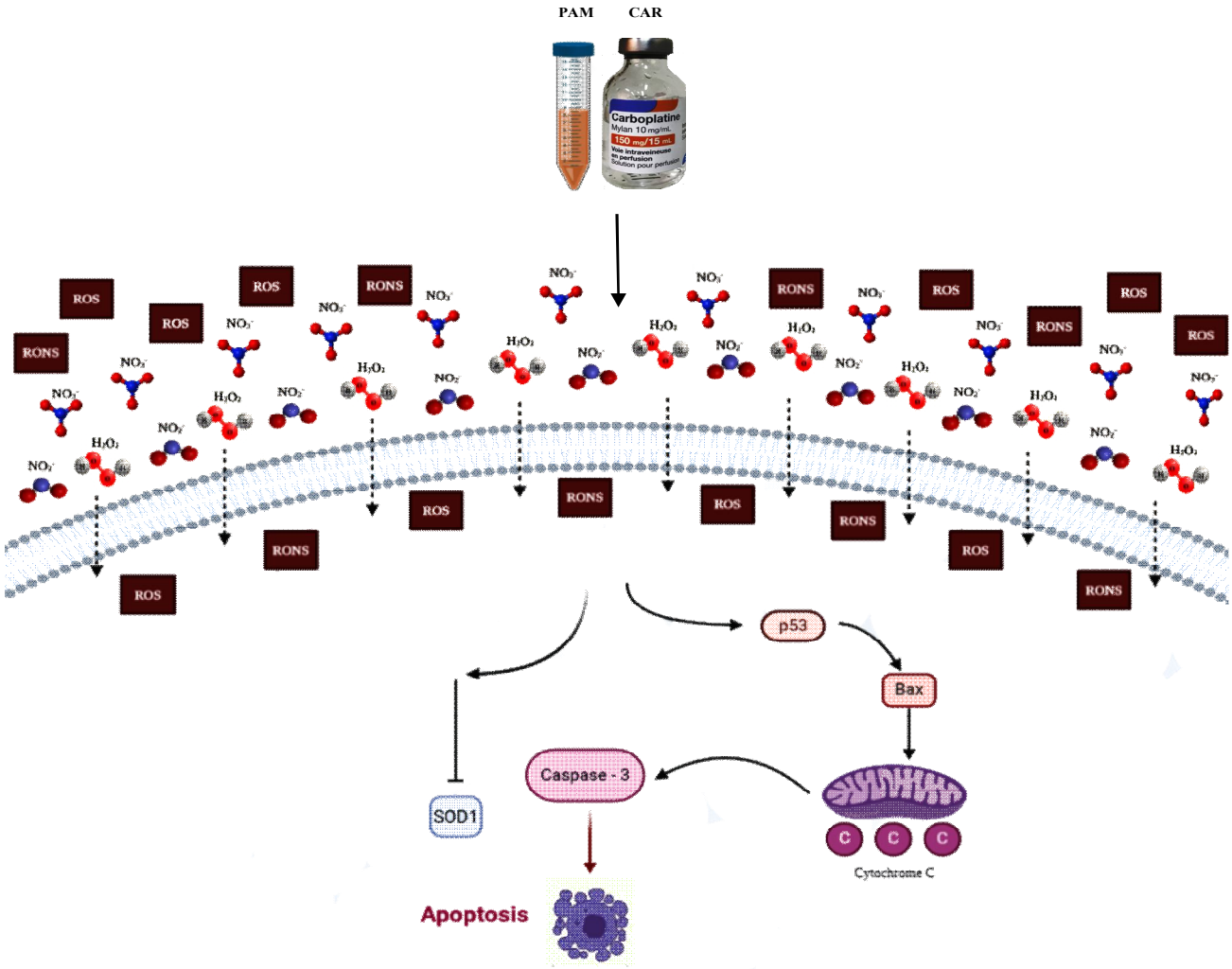

Fig. 4. Molecular mechanism of inhibition of the SOD1 and mitochondrial-related intrinsic apoptosis-inducing by PAM and CAR. Abbreviation: PAM, plasma-activated medium and CAR, carboplatin.

Wound healing and cancer treatment are among the most important of these challenges in which GP efficacy has been discovered both pre-clinically and clinically. The literature shows GP has potential efficacies for wound healing management and oncotherapy. It is should be noted that GP used for a specific application at a suitable dose. While high doses are required to kill cancer cells, low doses are required for wound healing. Given the extent and complex structure of cancer compared to wound healing, it seems that we have a long time to GP introduce as the fifth oncotherapeutic agent. In contrast, the use of plasma for wound healing has begun in some clinics as adjunctive therapy.

REFERENCES

[1] D. Traversi, A. Pulliero, A. Izzotti, E. Franchitti, L. Iacoviello, F. Gianfagna, A. Gialluisi, B. Izzi, A. Agodi, M. Barchitta, G.E. Calabrò, J. Pers. Med. 11 (2021) 135.

[2] E. Arvidsson, I. Švab, Z. Klemenc-Ketiš, Front. Med. 23 (2021) 158.
[3] K.C. de Castro, M.G. Campos, L.H. Mei, Int. J. Biol. Macromol. 173 (2021) 251.
[4] J. Zugazagoitia, C. Guedes, S. Ponce, I. Ferrer, S. Molina-Pinelo, L. Paz-Ares, Clin. Ther. 38 (2016) 1551.
[5] M. Ferrari, Nat. Rev. Cancer 5 (2005) 161.
[6] L. Teot, N. Ohura, Plast. Reconstr. Surg. 147 (2021) 9.
[7] T.N. Demidova-Rice, J.T. Durham, I.M. Herman, Adv. Wound Care. 1 (2012) 17.
[8] Y. Wang, J. Beekman, J. Hew, S. Jackson, A.C. Issler-Fisher, R. Parungao, S.S. Lajevardi, Z. Li, P.K. Maitz, Adv. Drug Deliv. Rev. 123 (2018) 3.
[9] J. Ahmed, M. Gultekinoglu, M. Edirisinghe, Biotechnol. Adv. 14 (2020) 107549.
[10] V. Alexandrescu (Ed.), Wound Healing: New Insights into Ancient Challenges. BoD-Books on Demand, 2016.
[11] J. Zugazagoitia, C. Guedes, S. Ponce, I. Ferrer, S. Molina-Pinelo, L. Paz-Ares, Clin. Ther. 38 (2016) 1551.
[12] C. Pucci, C. Martinelli, G. Ciofani, Ecancermedicalscience 13 (2019).
[13] A.J. Price, P. Ndom, E. Atenguena, J.P. Mambou Nouemssi, R.W. Ryder, Cancer 118 (2012) 3627.
[14] M. Rasouli, N. Fallah and K. (Ken) Ostrikov (December 28th 2020). Lung Cancer Oncotherapy through Novel Modalities: Gas Plasma and Nanoparticle Technologies [Online First], IntechOpen.
[15] D. Peer, J.M. Karp, S. Hong, O.C. Farokhzad, R. Margalit, R. Langer, Nat. Nanotechnol. 2 (2007) 751.
[16] T. Von Woedtke, S. Reuter, K. Masur, K.D. Weltmann, Phys. Rep. 530 (2013) 291.
[17] X. Lu, G.V. Naidis, M. Laroussi, S. Reuter, D.B. Graves, K. Ostrikov, Phys. Rep. 630 (2016) 1.
[18] G. Fridman, G. Friedman, A. Gutsol, A.B. Shekhter, V.N. Vasilets, A. Fridman, Plasma Process Polym. 5 (2008) 503.
[19] M. Laroussi, M.G. Kong, G. Morfill, W. Stolz (Eds.), Plasma Medicine: Applications of Low-temperature Gas Plasmas in Medicine and Biology. Cambridge University Press, 2012.
[20] K.D. Weltmann, T. Von Woedtke, Plasma Phys. Control. Fusion. 59 (2016) 14.
[21] X. Dai, K. Bazaka, D.J. Richard, E.R. Thompson, K.K. Ostrikov, Trends Biotechnol. 36 (2018) 1183.
[22] B. Stratmann, T.C. Costea, C. Nolte, J. Hiller, J. Schmidt, J. Reindel, K. Masur, W. Motz, J. Timm, W. Kerner, D. Tschoepe, JAMA Netw. Open. 3 (2020) e2010411.
[23] F.F. Chen, Introduction to Plasma Physics and Controlled Fusion. New York: Plenum Press; 1 (1984) 19.
[24] T. von Woedtke, S. Emmert, H.R. Metelmann, S. Rupf, K.D. Weltmann, Phys. Plasmas. 27 (2020) Jul 070601.
[25] A. Schmidt, S. Bekeschus, Antioxidants 7 (2018) 146.
[26] S. Bekeschus, P. Favia, E. Robert, T. von Woedtke, Plasma Process Polym. 16 (2019) 1800033.
[27] M. Keidar, D. Yan, I.I. Beilis, B. Trink, J.H. Sherman, Trends Biotechnol. 36 (2018) 586.
[28] E. Robert, V. Sarron, T. Darny, D. Riès, S. Dozias, J. Fontane, L. Joly, J.M. Pouvesle, Plasma Sources Sci. Technol. 23 (2014) 012003.
[29] Z. Machala, M. Janda, K. Hensel, I. Jedlovský, L. Leštinská, V. Foltin, V. Martišovitš, M. Morvova, J. Mol. Spectrosc. 243 (2007) 194.
[30] D. Yan, J.H. Sherman, M. Keidar, Oncotarget 8 (2017) 15977.
[31] P.J. Bruggeman, M.J. Kushner, B.R. Locke, J.G. Gardeniers, W.G. Graham, D.B. Graves, R.C. Hofman-Caris, D. Maric, J.P. Reid, E. Ceriani, D.F. Rivas, Plasma Sources Sci. Technol. 25 (2016) 053002.
[32] M. Ishaq, M. Evans, K. Ostrikov, Int. J. Cancer 134 (2014) 1517.
[33] D. Liu, E.J. Szili, K. Ostrikov, Plasma Process Polym. 17 (2020) 2000097.
[34] M. Keidar, A. Shashurin, O. Volotskova, M. Ann Stepp, P. Srinivasan, A. Sandler, B. Trink, Phys. Plasmas. 20 (2013) 057101.
[35] S.A. Guo, L.A. DiPietro, J. Dent. Res. 89 (2010) 219.

[36] S. Dhivya, V.V. Padma, E. Santhini, Bio. Medicine 5 (2015) 22.
[37] M. Pakyari, A. Farrokhi, M.K. Maharlooei, A. Ghahary, Adv. Wound Caref. 2 (2013) 215.
[38] J.G. Powers, C. Higham, K. Broussard, T.J. Phillips, J. Am. Acad. Dermatol. 74 (2016) 607.
[39] H. Hamedi, S. Moradi, S.M. Hudson, A.E. Tonelli, Carbohydr. Polym. 199 (2018) 445.
[40] R. Pereira, A. Carvalho, D.C. Vaz, M.H. Gil, A. Mendes, P. Bártolo, Int. J. Biol. Macromol. 52 (2013) 221.
[41] F. Gottrup, Am. J. Surg. 187 (2004) 38.
[42] D. Simões, S.P. Miguel, M.P. Ribeiro, P. Coutinho, Mendonça, I.J. Correia, Eur. J. Pharm. Biopharm. 127 (2018) 130.
[43] R.F. Pereira, P.J. Bartolo, Adv. Wound Care. 5 (2016) 208.
[44] D. Simões, S.P. Miguel, M.P. Ribeiro, P. Coutinho, A.G. Mendonça, I.J. Correia, Eur. J. Pharm. Biopharm. 127 (2018) 130.
[45] S. Sharifi, M.J. Hajipour, L. Gould, M. Mahmoudi, Mol. Pharm. 18 (2020) 550.
[46] A.J. Whittam, Z.N. Maan, D. Duscher, V.W. Wong, J.A. Barrera, M. Januszyk, G.C. Gurtner, Adv. Wound Caref. 5 (2016) 79.
[47] G. Busco, E. Robert, N. Chettouh-Hammas, J.M. Pouvesle, C. Grillon, Free Radic. Biol. Med. 161 (2020) 290.
[48] B. Haertel, T. Von Woedtke, K.D. Weltmann, U. Lindequist, Biomol. Ther. 22 (2014) 477.
[49] S. Bekeschus, A. Schmidt, K.D. Weltmann, T. von Woedtke, Clin. Plasma Med. 4 (2016) 19.
[50] T. Bernhardt, M.L. Semmler, M. Schäfer, S. Bekeschus, S. Emmert, L. Boeckmann, Oxid. Med. Cell. Longev. 2019 (2019).
[51] L. Gan, S. Zhang, D. Poorun, D. Liu, X. Lu, M. He, X. Duan, H. Chen, J. Dtsch. Dermatol. Ges. 16 (2018) 7.
[52] J. Gay-Mimbrera, M.C. García, B. Isla-Tejera, A. Rodero-Serrano, A.V. García-Nieto, J. Ruano. Adv. Ther. 33 (2016) 894.
[53] Y.S. Lee, M.H. Lee, H.J. Kim, H.R. Won, C.H. Kim, Sci. Rep. 7 (2017).
[54] S. Arndt, A. Schmidt, S. Karrer, T. von Woedtke, Clin. Plasma Med. 9 (2018) 24.
[55] S. Kalghatgi, G. Friedman, A. Fridman, A.M. Clyne, Ann. Biomed. Eng. 38 (2010) 748.
[56] G. Isbary, J. Heinlin, T. Shimizu, J.L. Zimmermann, G. Morfill, H.U. Schmidt, R. Monetti, B. Steffes, W. Bunk, Y. Li, T. Klaempfl, Br. J. Dermatol. 167 (2012) 404.
[57] R. He, Q. Li, W. Shen, T. Wang, H. Lu, J. Lu, F. Lu, M. Luo, J. Zhang, H. Gao, D. Wang, Int. Wound J. 17 (2020) 851.
[58] G. Daeschlein, S. Scholz, A. Arnold, S. von Podewils, H. Haase, S. Emmert, T. von Woedtke, K.D. Weltmann, M. Jünger, Plasma Process Polym. 9 (2012) 380.
[59] M.K. Singh, A. Ogino, M. Nagatsu, New J. Phys. 11 (2009) 115027.
[60] G. Daeschlein, S. Scholz, S. Emmert, S. von Podewils, H. Haase, T. von Woedtke, M. Junger, Plasma Med. 2 (2012) 33.
[61] XM. Shi, GM. Xu, GJ. Zhang, JR. Liu, YM. Wu, LG. Gao, Y. Yang, ZS. Chang, CW. Yao. Curr. Med. Sci. 38 (2018) 107.
[62] A. Schmidt, S. Bekeschus, K. Jarick, S. Hasse, T. von Woedtke, K. Wende, Oxid. Med. Cell. Longev. 2019 (2019).
[63] A. Schmidt, T. von Woedtke, S. Bekeschus, Oxid. Med. Cell. Longev. 2016 (2016).
[64] A. Schmidt, S. Bekeschus, Antioxidants 7 (2018) 146.
[65] M. Rasouli, N. Fallah and K. (Ken) Ostrikov (February 26th 2021). Nano Technology and Gas Plasma as Novel Therapeutic Strategies for Ovarian Cancer Oncotherapy [Online First], IntechOpen.
[66] G. Bauer, D. Sersenová, D.B. Graves, Z. Machala, Sci. Rep. 9 (2019).
[67] E. Robert, M. Vandamme, L. Brullé, S. Lerondel, A. Le Pape, V. Sarron, D. Riès, T. Darny, S. Dozias, G. Collet, C. Kieda, Clin. Plasma Med. 1 (2013) 8.
[68] D. Yan, Q. Wang, M. Adhikari, A. Malyavko, L. Lin, D.B. Zolotukhin, X. Yao, M. Kirschner, J.H. Sherman, M. Keidar, ACS Appl. Mater. Interfaces 12 (2020) 34548.

[69] D. Yan, A. Talbot, N. Nourmohammadi, J.H. Sherman, X. Cheng, M. Keidar, Biointerphases 10 (2015) 040801.

[70] M. Keidar, R. Walk, A. Shashurin, P. Srinivasan, A. Sandler, S. Dasgupta, R. Ravi, R. Guerrero-Preston, B. Trink. Br. J. Cancer 105 (2011) 1295.

[71] K. Ninomiya, T. Ishijima, M. Imamura, T. Yamahara, H. Enomoto, K. Takahashi, Y. Tanaka, Y. Uesugi, N. Shimizu, J. Phys. D Appl. Phys. 46 (2013) 425401.

[72] N. Kaushik, N. Uddin, G.B. Sim, Y.J. Hong, K.Y. Baik, C.H. Kim, S.J. Lee, N.K. Kaushik, E.H. Choi, Sci. Rep. 5 (2015).

[73] H. Tanaka, M. Mizuno, K. Ishikawa, K. Nakamura, H. Kajiyama, H. Kano, F. Kikkawa, M. Hori, Plasma Med. 1 (2011) 265.

[74] G.C. Kim, G.J. Kim, S.R. Park, S.M. Jeon, H.J. Seo, F. Iza, J.K Lee, J. Phys. D Appl. Phys. 42 (2008) 032005.

[75] C. Welz, S. Emmert, M. Canis, S. Becker, P. Baumeister, T. Shimizu, G.E. Morfill, U. Harréus, J.L. Zimmermann, PloS One 10 (2015) 0141827.

[76] M. Vandamme, E. Robert, S. Lerondel, V. Sarron, D. Ries, S. Dozias, J. Sobilo, D. Gosset, C. Kieda, B. Legrain, J.M. Pouvesle, Int. J. Cancer 130 (2012) 2185.

[77] M. Schuster, C. Seebauer, R. Rutkowski, A. Hauschild, F. Podmelle, C. Metelmann, B. Metelmann, T. von Woedtke, S. Hasse, K.D. Weltmann, H.R. Metelmann, J. Craniofac. Surg. 44 (2016) 1445.

[78] H.R. Metelmann, C. Seebauer, V. Miller, A. Fridman, G. Bauer, D.B. Graves, J.M. Pouvesle, R. Rutkowski, M. Schuster, S. Bekeschus, K. Wende, Clin. Plasma Med. 9 (2018) 6.

[79] M. Rasouli, H. Mehdian, K. Hajisharifi, E. Amini, K. Ostrikov, E. Robert, Research Square. (2020).