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PLASMA BIOMEDICINE: MODERN STATE-OF-ART AND PERSPECTIVES IN REGENERATIVE MEDICINE

Martusevich A.K.[1,2]*, Fedotova A.S.[1], Surovegina A.V.[1,2], Nazarov V.V.[1]

[1] Laboratory of Medical Biophysics Privolzhsky Research Medical University, Nizhny Novgorod, Russia
[2] Nizhny Novgorod State Agrotechnological University, Nizhny Novgorod, Russia

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Abstract

The purpose of the review was a comprehensive analysis of the biological effects and applications of cold plasma.

First of all, physical principles of cold atmospheric plasma, including generation of reactive oxygen and nitrogen species as intermediates, were discussed. The analysis of the specialized literature on plasma medicine as an innovative interdisciplinary direction allowed us to show the physical mechanisms of biological effects of cold plasma associated with the modulation of free radical processes in the biological objects. That is why correction of oxidative stress and other disorders of redox balance was determined as direct target of the effect of studied factor.

Among the most significant aspects of the biological action of cold plasma, antibacterial and pro-regenerative activity, as well as modulation of apoptosis, should be cited. On this basis, the factor in question determines its application in oncology, surgery, dermatology and other fields of medicine.

One of the most important effects of cold plasma was its antibacterial and antifungal activity, which in useful for wound healing, sterilization etc. Special attention was paid to possibilities of cold plasma therapy in combustiology. Molecular, tissue and systemic mechanisms of sanogenic effects of cold plasma was demonstrated and analyzed.

Results of own studied in this field was observed. Further discovery of the biological effects of cold plasma can significantly expand the range of its medical applications.

Keywords: *cold plasma, biological effects, reactive oxygen species, oxidative stress.*

Introduction

Plasma medicine is the direction of using low-temperature atmospheric pressure plasma to generate controlled amounts of specific chemically active substances that are transported to interact with biological targets, including cells and tissues [*Laroussi M, 2020*]. Plasma medicine is an interdisciplinary research field combining plasma physics, biochemical and biological sciences and clinical medicine [*von Woedtke T et al., 2019*]. This area was formed in the mid-1990s on the basis of a number of experiments that showed that low-temperature plasma has effective bactericidal properties [*Laroussi M, 1996; Herrmann H et al., 1999*; *Laroussi M et al., 2000*]. The antibacterial activity of cold plasma has been the subject of research for several years and has been shown in experiments both in vitro and in vivo [*Kelly-Wintenberg K et al., 1998; Laroussi M et al., 2000*].

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Address for Correspondence:
Andrew K. Martusevich, PhD
Privolzhsky Research Medical University
10/1 Minin square, Nizhny Novgorod, Russia
Tel. +7-909-144-92-82
E-mail: cryst-mart@yandex.ru

Currently, it is known that the biological effects of cold plasma are mainly based on the action of reactive oxygen and nitrogen forms supported by electric fields and ultraviolet radiation. In addition to its antimicrobial activity, the effect of physical plasma on mammalian cells can lead to either stimulation or inhibition of cell functions. However, the biological effects and mechanisms of action of cold plasma on cells and tissues have not yet been fully studied and require a comprehensive approach to their analysis in order to form general ideas about the nature of the biosystem's response to the effects of cold plasma.

The purpose of the review is a comprehensive review of the biological effects and applications of cold plasma.

MODERN IDEAS ABOUT COLD ATMOSPHERIC PLASMA

Physical plasma is a special excited gas state, sometimes called the "fourth state of matter", following solid, liquid and gaseous. It can be generated by a continuous supply of energy to atoms or molecules of a neutral gas until an excited state is reached [*Kong M et al., 2009*].

Radicals and electrons formed during plasma formation can be both short-lived and long-lived. These radicals or electrons reach the solution and enter into many complex reactions, as a result of which other short-lived and long-lived radicals are formed. Short-lived radicals include superoxide (O_2^-), nitrite (NO), atomic oxygen (O), ozone (O_3), hydroxyl radical (•OH^-), singlet oxygen ($^1O_2$), and peroxynitrite ($ONOO^-$). Long-lived species include hydrogen peroxide (H_2O_2) and nitrite (NO_2^-) [*Dubuc A et al., 2018*].

It is known that reactive particles formed inside the plasma or as a result of plasma interaction with the environment are the main components of chemical reactivity and the most important components responsible for biological plasma effects [*von Woedtke T et al., 2019*].

Plasma is classified into two categories based on temperature, namely "thermal" and "non-thermal", or "cold", atmospheric plasma. Cold atmospheric plasma is formed by treating the gas stream with a high-voltage electric field [*Hoffmann C et al., 2013*].

APPLICATION OF COLD ATMOSPHERIC PLASMA

Cold atmospheric plasma has received considerable attention for its potential biomedical applications. New applications include wound healing, sterilization of infected tissues, inactivation of microorganisms, skin regeneration and cancer therapy. This has collectively been called "plasma medicine". Plasma medicine is a rapidly developing interdisciplinary field combining engineering, physical, biochemical and biological sciences [*Kong M et al., 2009*]. To create a cold plasma, special generators based on various methods of ionization of the gas stream are currently used (Fig. 1).

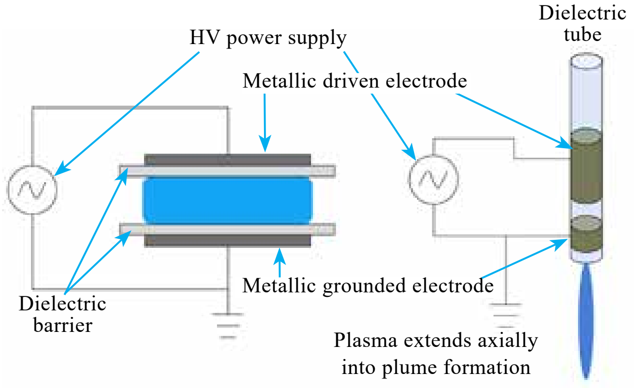

FIGURE 1. Basic configurations of cold atmospheric pressure plasma sources: a) dielectric barrier discharge; b) cold plasma jet [*O'Connor N et al., 2014*]

The use of plasma for processing medical materials or devices is an important subject of research and has been used for several years. The focus of these studies is focused on the use of plasma technologies in the correction of the state of cells and tissues [*Oleinik A, 2011; Martusevich A et al., 2020a; b; 2021a*]. In addition to its antimicrobial activity, the effect of physical plasma on mammalian cells may cause stimulation or inhibition of cellular function. Consequently, most of the research and primary medical use of physical plasma is focused on the treatment of wounds and cancers [*von Woedtke T et al., 2019; 2020*].

One of the main advantages of the biomedical application of plasma is that the active components, such as reactive oxygen and nitrogen species, are generated locally and only for the required duration of application primarily by a physical process. The understanding that exposure to cold atmospheric plasma can lead either to stimulation of cells and tissues, or to cell death, depending on the conditions of exposure (for example, treatment time), is very well consistent with the theory of oxidative stress (Fig. 2). According to this, oxida-

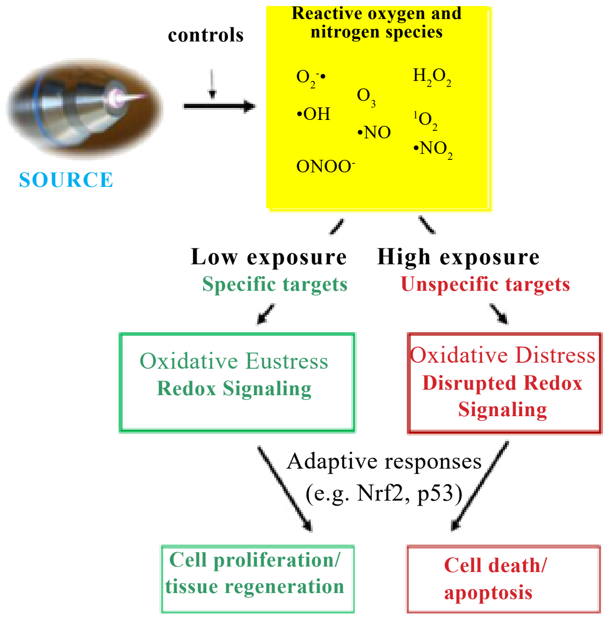

FIGURE 2. Mechanisms of oxidative stress caused by exposure to cold atmospheric plasma [von Woedtke T et al., 2019]

tive stress can be differentiated between oxidative eustress and oxidative distress depending on low or high oxidant exposure [*von Woedtke T et al., 2019; 2020*].

INACTIVATION OF MICROORGANISMS USING COLD ATMOSPHERIC PLASMA

Ultraviolet radiation in the range of 260-265 *nm* creates damage in DNA in the form of cyclobutane pyrimidine dimers, which inhibit the ability of bacteria to replicate. It induces further changes in the molecular content (proteins and lipids) of the cell, as well as the generation of reactive oxygen species. They can lead to damage to other cellular functions, such as lipid peroxidation, affecting mainly the phospholipid bilayer and other internal lipids [*Kong M et al., 2009*].

The addition of small amounts of O_2 or air to the helium plasma leads to the appearance of numerous sources of reactive oxygen species (ROS) and reactive nitrogen species (RNS). The addition of a small amount of air or oxygen, for example, leads to the local formation of large amounts of ozone (O_3), atomic oxygen (O), superoxide (*O_2^-), hydroxyl radicals (*OH^-), nitric oxide (NO), hydrogen peroxide (H_2O_2) and other active molecules that are known to have a bactericidal effect. The molecules listed above attack the bacterial structure in various ways. Reactive oxygen species, such as atomic oxygen and *OH^-, disrupt the outer cell envelope, thereby exposing the cell membrane. Plasma radicals also affect unsaturated fatty acids in the phospholipid bilayer, which are susceptible to attack by most ROS [*O'Connor N et al., 2014*].

The oxidation of cell proteins with atomic oxygen, *OH^- or *O_2^- changes their structure and causes functional changes that can disrupt cellular metabolism, preventing the replication of basic proteins, therefore slowing down cellular metabolism. At the same time, bactericidal and other damaging effects are realized under the action of high concentrations of ROS and RNS. At low concentrations, most ROS have a positive effect on cell functionality, for example, inhibition of peroxidation or neutralization of other reactive components [*Kong M et al., 2009*].

COLD ATMOSPHERIC PLASMA IN ONCOLOGY

Plasma induces both physical effects (generation of ultraviolet radiation and electromagnetic fields) and chemical effects (synthesis of ROS). At that time, the resulting ions can induce a change in the cell membrane, an increase in intracellular ROS, a decrease in antioxidant potential and inhibition of double-stranded DNA, and then apoptosis [*Dubuc A et al., 2018*].

Reactive oxygen species activate the internal apoptotic pathway due to their interaction with mitochondrial pore proteins (Fig. 3) [*Tsujimoto Y, Shimizu S, 2007*]. In addition, it is known that ROS (H_2O_2) also specifically induce apoptosis via the FAS receptor [*Strasser A, Newton K, 1999*; *Yin X, 2000*]. In addition, FAS/TNF-R1 can cause apop-

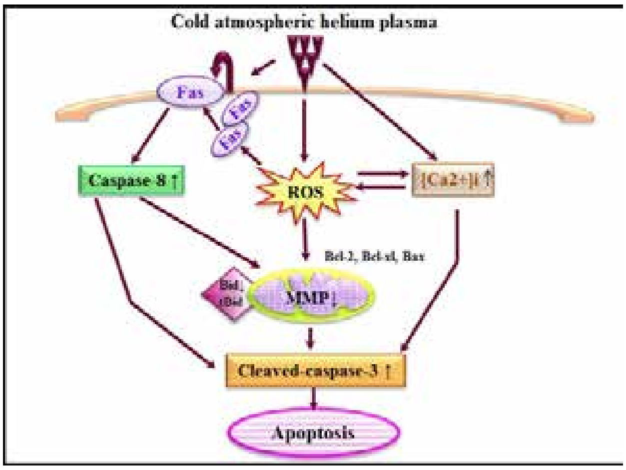

FIGURE 3. Activation pathways of apoptosis induced by cold atmospheric plasma based on helium [Jawaid P et al., 2016]

tosis through direct recruitment of the cascade of caspases or through mitochondria by activating caspase-8 and the Bid protein [*Nitobe J et al., 2003*]. The internal pathway includes disruption of the mitochondrial membrane, release of mitochondrial proteins, including Cytochrome-C, increase in [Ca^{2+}], activation of Bcl-2 and p53 family proteins [*Wang X, 2001*]. These two apoptotic pathways eventually trigger effector caspases, which leads to cellular compression, DNA fragmentation, and may be associated with caspase-8-mediated Bid cleavage, which causes activation of the mitochondrial pathway [*Jawaid P et al., 2016*].

One of the main advantages of cold plasma in comparison with other methods of treatment is the potential tropicity in relation to cancer cells [*Guerrero-Preston R et al., 2014; Yan D et al., 2015*]. Several hypotheses can be put forward to explain this phenomenon. Firstly, it has been shown that the training effect of hyperoxidation increases the resistance of healthy cells, but not tumor cells [*Yan D et al., 2015*]. Secondly, cancer cells show a higher amount of aquaporin on their membranes, which ensures the transport of RNS between the intracellular and extracellular spaces [*Yan D et al., 2015*]. Finally, the diffusion of RNS is related to the cholesterol composition of the cell membrane. Peroxidation of membrane lipids leads to the formation of pores and increases the diffusion of reactive molecules. A lower proportion of cholesterol in tumor cells leads to the fact that cells become less resistant to peroxidation, followed by increased diffusion of ROS and oxidative stress [*Van der Paal J et al., 2017*].

Thus, cold plasma-induced cell death in the treatment of cancer is one of the most interesting areas of research on the use of cold plasma. It can be predicted that in most cases cold plasma therapy will be included in complex algorithms for the treatment of neoplasms. In addition to its combination with surgical resection of the tumor or immunotherapy, other investigated options are combinations of the factor in question with radiation therapy, pulse fields and chemotherapy [*von Woedtke T et al., 2020*].

COLD PLASMA IN DERMATOLOGY AND REGENERATIVE MEDICINE

Cold atmospheric plasma can effectively inactivate infectious microorganisms within a few minutes without causing skin allergic reactions or resistance to plasma exposure (Fig. 4). It has been suggested that the antibacterial effect of plasma is

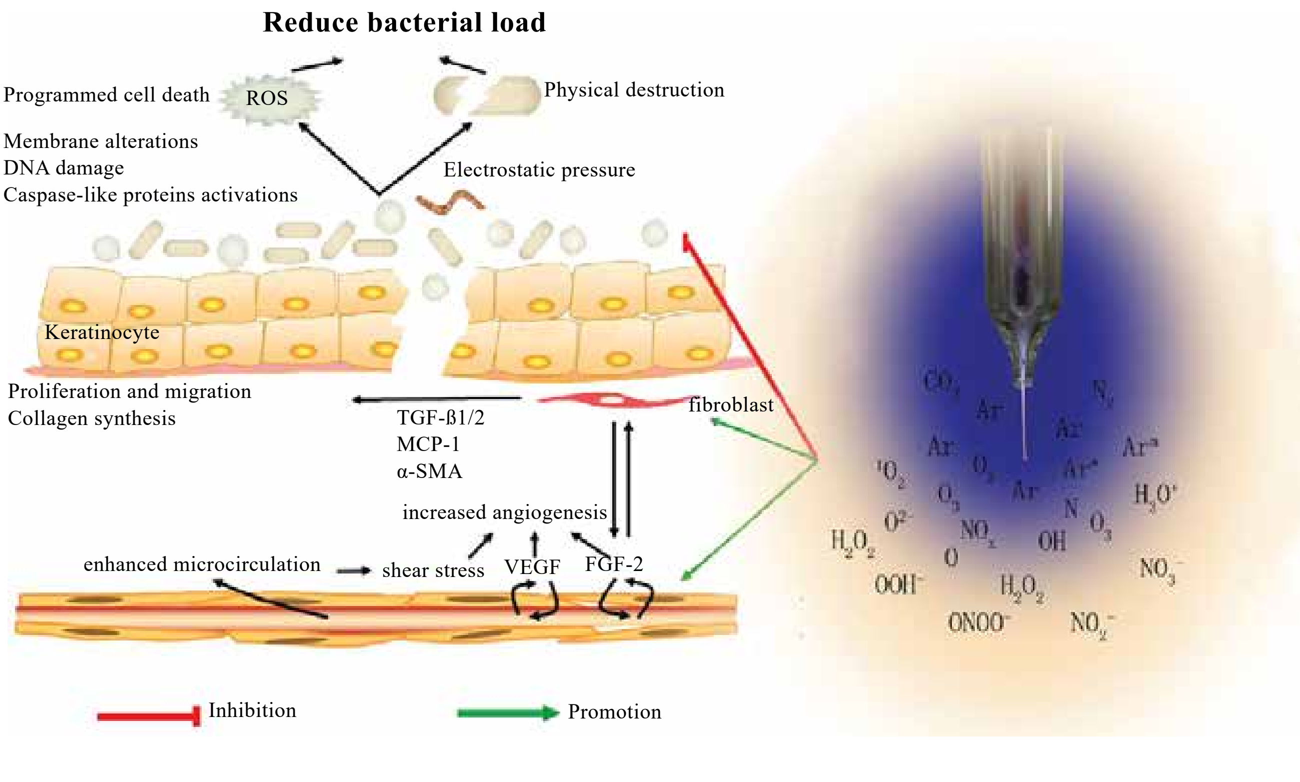

***FIGURE 4** The effect of cold atmospheric plasma on wound healing* [*Gan L et al., 2018*]

realized by activating the following mechanisms: stimulation of lipid peroxidation, proteins and DNA; activation of programmed bacterial death; direct mechanical lysis of cells under the action of electrostatic pressure [*Lunov O et al., 2015*]. Changes in plasma-induced environmental conditions, such as pH, also lead to inactivation of biomolecules. Plasma treatment has been found to reduce bacterial load and promote wound healing [*Heinlin J et al., 2011*].

Cold atmospheric plasma can affect the cells involved in wound healing [*Gan L et al., 2018*]. Optimal plasma doses can promote the proliferation and migration of keratinocytes and fibroblasts, as well as induce the expression of genes related to wound healing, such as type I collagen, transforming growth factors (TGF-β1 and 2) and α-actin (α-SMA). Studies show that plasma can improve wound vascularization. Plasma-mediated release of ROS and fibroblast growth factor-2 can promote endotheliocyte migration and proliferation [*Wende K et al., 2014; Lotfy K, 2016; Mizuno K et al., 2017*]. In addition, oxygen saturation of skin cells and microcirculation can be enhanced, contributing to neoangiogenesis. New vascular networks and activated capillary blood flow increase local oxygen saturation and nutrient intake, which also promotes wound healing.

The immune system also plays an important role in the regeneration process. In vitro studies have shown that short-term plasma treatment gives some stimulating effects that cause immune cells to actively multiply and function, maintaining antimicrobial protection when pathogens are removed [*Stoffels E et al., 2002; Scholtz V et al., 2015; Gan L et al., 2018*].

Thus, plasma treatment of wound sites reduces bacterial load, promotes the action, proliferation and migration of cells associated with wound healing, improves angiogenesis and enhances local microcirculation for sufficient supply of oxygen and nutrients. All of the above leads to improved wound healing [*Pompl P et al., 2009; Pouvesle J, Robert É, 2013; Vijayarangan V et al., 2017; Yan D et al., 2017; Gan L et al., 2018*; *Martusevich A et al., 2021b*].

Perspectives of the use of cold atmospheric plasma in combustiology

The above-mentioned effects of cold plasma (antibacterial activity and stimulation of regenerative processes) in combination are extremely significant for the treatment of wounds, including burns [*García-Alcantara E et al., 2013; Hung Y et al., 2016; Kubinova S et al., 2017; Martusevich A et al., 2022a*]. On this basis, it is of interest to evaluate the sanogenetic potential of cold atmospheric plasma in combustiology. Currently, there are few publications in this direction, but they allow us to obtain certain information about the preliminary effectiveness of cold plasma therapy in the treatment of both experimental and real burns.

Thus, in a study on pseudomonad strains isolated from animals with experimental burn, it was shown that cold plasma treatment significantly inhibits the growth of this microorganism on various nutrient media [*Abbasi E et al., 2021*]. In addition, the authors have established a similar effect in flushes from the wound surface, which was affected by a cold plasma flow. This confirms the antibacterial activity of the factor, allowing ignoring the problem of antibiotic resistance of microorganisms colonizing in the wound [*Bagheri M et al., 2023*]. It should be noted that the antibacterial properties of cold plasma are nonspecific and are realized for other pathogens (in particular, Candida albicans, Escherichia coli, etc. [*Lee O et al., 2016*]) Some researchers note that the decrease in colonization of wounds is less pronounced than when treated with antibacterial solutions [*Bagheri M et al., 2023*], however, the treatment regimen used allows for simultaneous activation of regenerative processes. In particular, a 1.63-fold decrease in the necrosis zone was revealed by 7 days after modeling thermal trauma using cold plasma therapy, and the area of deep necrosis is reduced even more significantly (28% vs 67%) [*Lee O et al., 2019*].

The modulating effect of cold plasma on inflammation processes associated with activation of neutrophil migration into wound tissues by day 7 of the post-burn period and accelerated replacement by macrophages by day 21 has also been demonstrated [*Souza L et al., 2020*]. These effects are caused by an increase in the production of pro-inflammatory cytokines (IL-1β, TNF-α and IL-17), and the intensity of the inflammatory reaction is additionally controlled by anti-inflammatory regulators (IL-10 and TGF-β1) [*Souza L et al., 2020*]. These events provide accelerated healing of the skin defect, inducing vascular bed restructuring and fibrillogenesis. Our experiments have also confirmed the formation of positive shifts in the functioning of microcirculation both in the wound tissues and in the near-wound zone [*Martusevich A et al., 2022b*]. They include not only the intensification of blood flow through small-diameter vessels, but also the activation of the endothelial component of microcirculation regulation, as well as a decrease in blood discharge through bypass routes. Such an action is complemented by systemic effects, including the relief of the phenomena of pronounced oxidative stress in the blood of animals with thermal trauma [*Martusevich A et al., 2021c*].

There are certain data on the clinical efficacy of cold plasma therapy in patients with burns. In particular, Betancourt-Ángeles M. et al. (2017) pointed to the acceleration of burn wound healing and pain relief after the second procedure. Our results also confirm this sanogenetic effect.

Finally, cold plasma can be used for pretreatment of wound coatings, including those containing nanoparticles, which increases their mechanical properties, biocompatibility, release, etc. [*Bolouki N et al., 2021*].

CONCLUSION

The analysis of the profile literature on plasma medicine as an innovative interdisciplinary direction allowed us to show the physical mechanisms of biological effects of cold plasma associated with the induction of the formation of reactive oxygen and nitrogen forms in a biological object. Among the most significant aspects of the biological action of cold plasma, antibacterial and pro-regenerative activity, as well as modulation of apoptosis, should be cited. On this basis, the factor in question determines its application in oncology, surgery, dermatology and other fields of medicine. Further discovery of the biological effects of cold plasma can significantly expand the range of its medical applications.

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Phones:

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