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Short Communication

Plasma oncology - Physical plasma as innovative tumor therapy

Matthias B. Stope*

Department of Gynecology and Gynecological Oncology, University Hospital Bonn, Bonn, Germany

*Author for correspondence:
Email: matthias.stope@ukbonn.de

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Abstract

Physical applications are an integral part of diagnostic and therapeutic procedures and modern medicine would be unthinkable without them. With physical plasma, a technology that has long been used for technical purposes has found its way into medical applications. The use of cold physical plasmas in oncological therapy appears to be of particular interest. First investigations indicate a variety of anticancer properties such as antiproliferative, antimetatstatic, and proapoptotic effects on tumor cells. Especially in combination with classical anti-cancer strategies such as surgical resection and chemotherapy, cold plasma treatment could provide an innovative and promising option for the oncology of the future.

Keywords: Physical plasma, Plasma medicine, Plasma oncology

Introduction

In medical diagnostics, complex physical techniques are state of the art and everyday clinical practice would be unthinkable without them. But also in the field of therapeutic interventions there are a number of physical procedures. For example, ionizing radiation is used in oncology and non-ionizing radiation in dermatological (UV light) and photodynamic therapies (laser). Similarly, electrosurgical and laser procedures are well established in surgery. The basis of all these methods is the interaction of physical noxious agents with biological tissue, which consequently leads to the desired medical effects. Currently, another physical procedure is being introduced for clinical application, treatment with physical plasma. This is a highly reactive, ionized gas consisting of electrically neutral particles including radicals, charged particles, free electrons and electromagnetic radiation.

Thermal and Non-thermal Physical Plasma

Physical plasma is present in nature (celestial bodies, lightning) and has been used technically for a long time (energy-saving lamps, plasma screens, surface engineering processes) [1]. There are different technical principles for the production of plasma. The dielectric barrier discharge and the plasma jet. In addition, various carrier gases such as argon, helium, nitrogen, heliox (helium-oxygen mixture) and air can be used to generate plasma [2]. The plasmas used in technical applications are usually thermal (hot) plasmas with temperatures ranging from slightly below 100°C to over 1,000°C. Furthermore, these technical plasmas are commonly used under defined pressure conditions well above (high-pressure plasma) or below (low-pressure plasma) atmospheric pressure [2]. For medical applications, however, only physical plasmas under atmospheric pressure can be used, since neither the entire patient nor individual body parts can be exposed to extreme pressure conditions. These plasmas are called atmospheric pressure plasmas and have been used in medicine for some time. Hot atmospheric pressure plasmas with temperatures in the range of about 100°C are used in surgical procedures for coagulation and obliteration of (malignant) tissue areas [3-6]. However, the thermal properties of the plasmas applied are of importance here; specific biological effects are not achieved at hot atmospheric pressure plasmas.

The field of plasma medicine made a great leap forward with the technical development of devices that produce non-thermal (cold) plasmas whose temperature is only slightly above body temperature. Such atmospheric pressure plasma devices produce a cold atmospheric plasma (CAP) and can be applied to patients without thermal irritation. This is achieved because the plasma is generated in

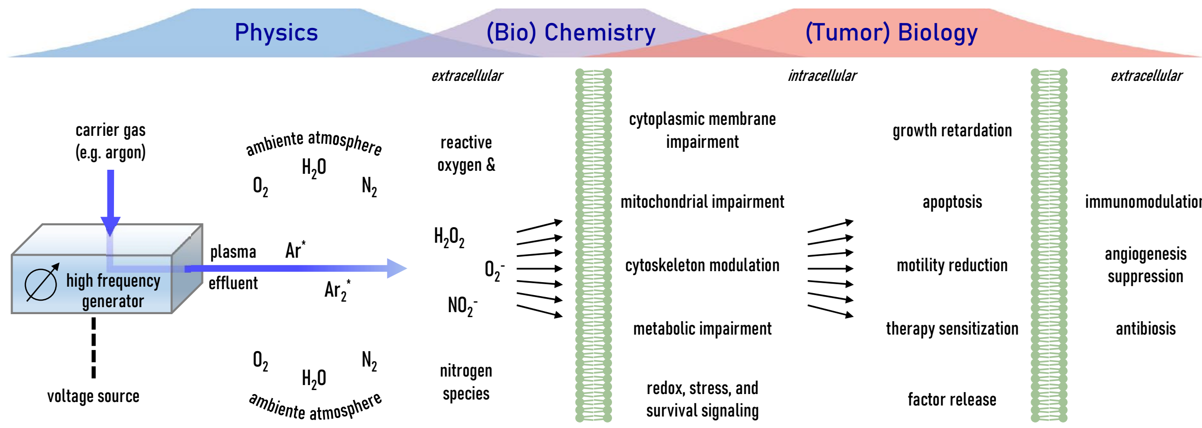

Figure 1: Mode of action of an oncological therapy with cold physical plasma using an argon plasma jet. The energization of the carrier gas argon by a high-frequency generator leads to the excitation of the argon atoms and a transfer of energy to atoms and molecules of the ambient air. The resulting high levels of reactive oxygen and nitrogen species are primarily responsible for the biological effect of cold plasmas. They can lead to disturbances of the cytoplasmic membrane, mitochondria, cytoskeleton, and metabolism. Furthermore, cellular stress cascades are induced, which correlate with various cell responses such as growth retardation, apoptosis, motility reduction, resensitization, and release of regulatory factors. By releasing cellular molecules, CAP can also indirectly affect cells in the tumor microenvironment, resulting in modulation of the immune system, inhibition of vascularization or antibiotic effects.

a high-frequency alternating field and thus the time is too short to transfer the kinetic energy of accelerated electrons to atoms by collision [7].

Biological Reactivity of Cold Physical Plasma

At the interface of CAP and ambient atmosphere, N_2, O_2 and H_2O molecules from the ambient air are cleaved, ionized or transformed into excited states. These reactive species react further. Concentration and composition of this mixture of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are therefore variable and change depending on the (reaction) time and localization in the CAP flame. For example, 87 reaction pathways have been described how NO_2 can be formed from primary ROS alone [8,9].

ROS are the crucial biologically active factors in the application of CAP and cause a wide variety of cellular responses (Figure 1). Due to their thermodynamic properties, ROS are more reactive than molecular oxygen [10]. Oxygen radicals react in one-electron reactions, which take place much faster than more complex multi-stage redox reactions. Especially radical species like singlet oxygen ($^1O_2$), hyperoxide anion radicals (O_2•$^-$), hydroxyl radicals (OH•$^-$), and hydroperoxides (R-OOH) are very unstable and therefore very short-lived particles. Non-radical oxidants, such as hypochlorous acid (HOCl) or hydrogen peroxide (H_2O_2), are relatively long-lived [11].

The cellular detoxification system for ROS consists of enzymatic and non-enzymatic radical scavengers and antioxidants as well as DNA repair mechanisms [12]. Antioxidative enzymes act by breaking down oxygen radicals. Catalases catalyze the conversion of H_2O_2 to oxygen (O_2) and water (H_2O) [13], peroxiredoxins catalyze the reduction of hydroperoxides [14], and sulfhydryl antioxidants such as glutathione contain a cysteine sulfhydryl group that can fill the free electron gap of radical species by giving off an electron [15]. Subsequently, the gluthation is oxidized to glutathione disulfide. The steady state of the cellular redox system is a highly dynamic system and ensures redox homeostasis [10].

In low physiological concentrations, ROS are intracellular signal mediators and can control signaling cascades through posttranslational chemical modifications of signaling proteins, for example in cell differentiation [10,16]. However, high ROS concentrations damage the cell (oxidative stress) [17]. If the cellular ROS detoxification system is overloaded, reactions with cellular structures such as DNA, proteins, or lipids occur [18], which may even lead to the induction of apoptosis [18,19].

Mainly due to these biological ROS effects, CAP has pronounced antimicrobial and anti-inflammatory properties. CAP treatment has therefore long been part of the therapy of wound healing disorders and chronic wounds [20]. In CAP treatment of chronic wounds, the bacterial count in the wound is reduced and wound healing is improved. The reduction of the microbial load applies to a large number of different microorganisms including multi-resistant pathogens. In addition, treatment with CAP does not lead to the allergic reactions and resistances that regularly occur under antibiotics [21]. Since the effective components of CAP are highly reactive chemical particles (ROS, RNS), genotoxic effects can be assumed. However, numerous studies have been conducted on the mutagenicity of CAP in eukaryotic cells and there is no evidence that CAP treatment induces mutations [22,23].

Immunological Reactivity of Cold Physical Plasma

Very limited knowledge is available about the impact of CAP on immunological mechanisms. This seems even more relevant, because especially the latest immunotherapeutic strategies in oncology are very promising. First immunological studies have shown that CAP treatment can modulate the expression and release of immunologically active factors (chemokines, cytokines, interleukins, growth factors, TNF superfamily members) in tumor cells [24-27]. Subsequently, activation of myeolide cells, differentiation into cytotoxic T cells, and re-infiltration of cytotoxic T cells into new tumor tissue was observed [28,29]. It can therefore be assumed that CAP treatment not only leads to cell death and growth retardation of tumor cells, but also provides tumor biological positive effects. This might lead to both immunogenic cancer cell death and anticancer immunity [30].

Cold Physical Plasma in Oncological Therapy - Plasma Oncology

Another innovative and very promising application is the use of CAP in oncological therapy [31,32]. Various studies show the antiproliferative and antimetatstatic effects of CAP on different cancer cell lines, including tumor cells of bone, skin, breast, ovary, and lung [33-37]. Furthermore, data show that, in addition to the intraoperative application of CAP, a combination with local chemotherapy is significantly more effective than the individual therapeutic procedures [38]. This could be used in particular to effectively inactivate chemoresistant tumors. At the molecular level, numerous effects have been described so far that contribute to the anti-oncogenic potential of CAP. These include disruption of membrane integrity and metabolism, manipulation of cellular (redox) signaling cascades, inhibition of angiogenesis, and induction of apoptosis [39-42].

Systematic clinical studies on the use of CAP in the treatment of solid tumors are still pending. However, the available experimental data indicate beyond doubt that the use of CAP represents an excellent complement to existing therapeutic procedures. First and foremost, an intraoperative use of CAP would be conceivable. After surgical resection of the tumor, this could be used to inactivate areas that are difficult to reach. Furthermore, CAP treatment of critical tumor areas in the immediate proximity of nerves or adjacent organs would be advantageous. Since ROS and RNS react in the tissue, CAP only has a local effect. This additionally reduces the risk of systemic effects such as those related to chemotherapeutic agents. Due to the increased permeability of the membrane, the combination of CAP treatment with a local administration of cytostatic drugs would also make sense. This would allow already resistant tumor cells to be sensitized. In addition, a dose reduction of the chemotherapeutic agent would be possible, which in turn would reduce side effects. Last but not least, due to its antimicrobial and wound healing promoting effects, an intraoperative CAP treatment would also contribute to reducing postoperative complications. All these applications concern open surgery. Currently, however, work is also in progress on CAP devices that can be used endoscopically, which would again significantly expand the application horizon. There is therefore a strong indication that in the tumor surgery of the future, treatment with CAP will also contribute to anti-oncogenic therapy.

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