Review Article

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Medical applications of nonthermal atmospheric pressure plasma in dermatology

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Summary

Plasma is an ionized gas that consists of positively and negatively charged particles, neutral atoms, and photons. Recent developments in plasma sources have made it possible to generate room-temperature plasma in the "open air", thus enabling the application of plasma in vivo. Using nonthermal plasma, active agents can be efficiently delivered to target cells without creating thermal damage. Also known as cold atmospheric pressure plasma (CAP), nonthermal atmospheric pressure plasma offers innovative medical applications. In this context, it has also gained wide attention in the field of dermatology. The complex and variable mixture of active agents in plasma – predominantly reactive oxygen and nitrogen species (ROS, RNS) – can control or trigger complex biochemical reactions, achieving the desired effects in a dose-dependent manner. The objective of the present review is to present potential applications of plasma in dermatology and analyze its potential mechanisms of action.

Introduction

Plasma is the fourth state of matter, consisting of charged particles (electrons and ions), neutral atoms, and photons; it has a net neutral charge. In general, it can be created by adding energy to a gas or gas mixture. Artificial plasma can be classified based on gas pressure (low-pressure vs. atmospheric pressure plasma) or based on temperature (thermal/hot vs. nonthermal/cold). Medical applications initially used plasma in thermal equilibrium; it relied on thermal energy for tissue removal, cauterization, and disinfection of thermally stable medical instruments. It was therefore not suitable for heat-sensitive substances, much less in vivo therapy. Recent advances in new plasma sources, which are able to generate CAP in open space under atmospheric pressure and at almost room temperature, has allowed for direct contact between plasma and the human body without causing thermal damage [1–3]. The fact that various CAP sources are currently being CE-certified as medical devices and that relevant clinical trials have been published is likely to further promote the use of plasma in routine clinical practice [4–6]. In general, the medical application of man-made CAP can be divided into two main types: direct plasma therapy and indirect plasma therapy, depending on the excitation mode [7]. Two basic principles of CAP sources are commonly used in experimental research and practical application: dielectric barrier discharges (DBD) and atmospheric pressure plasma jets (APPJ) (Figure 1), which are also the main CAP sources used for the presentation of potential plasma applications in this article. From a practical point of view, both DBD and APPJ devices have their advantages and disadvantages. When using DBD – a direct plasma source – the treatment area is larger but the device has to be held at close distance to the target surface. In addition, the current generated passes through the body as the treated tissue acts as one of the plasma

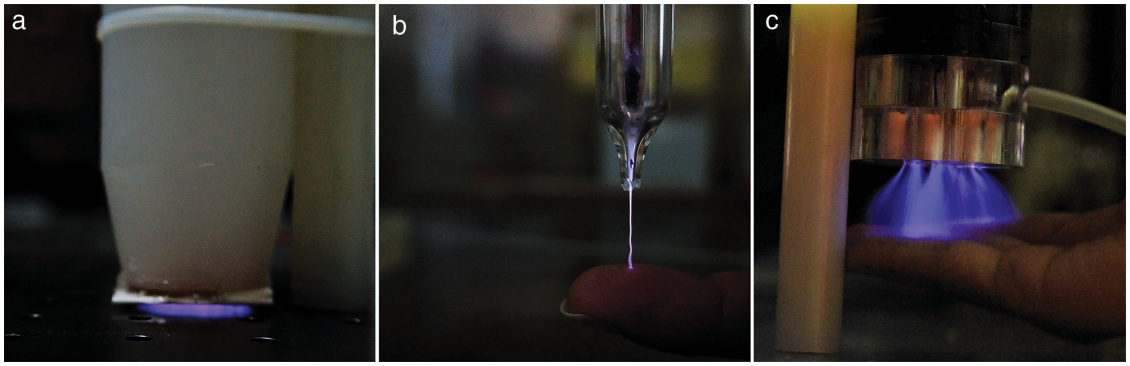

Figure 1 Images of various CAP devices used by our team. Floating electrode dielectric barrier discharge (FE-DBD) (a). Atmospheric pressure plasma jet (APPJ) (b). Atmospheric pressure plasma jet arrays (c).

electrodes. When using APPJ – an indirect plasma source – the distance between the device and the area to be treated is not as critical. Here, active agents are generated and precisely transported into small structures without the body having to act as a plasma electrode. However, the treatment of larger areas requires moving the plasma jet, which is inconvenient and results in inhomogeneous application [6–8]. Fortunately, cold atmospheric pressure plasma jet arrays able to treat larger areas are currently being studied as shown in Figure 1. Furthermore, liquid irradiated by plasma for a specified time, known as plasma-activated medium (PAM), has comparative biological effects and relatively long-lasting reactive species. PAM functions like plasma chemotherapy, thus broadening the potential applications of plasma. Therefore, both the direct and indirect interaction of plasma with biological targets offer an innovative therapeutic approach in clinical application [9, 10].

A number of fundamental research and clinical trials have demonstrated the huge clinical potential of plasma, including sterilization of living and nonliving surfaces [11–13], promotion of wound healing, as well as treatment of cancer [10, 14–16] and various skin diseases [4, 17–19]; the use of plasma is also characterized by good tolerability and biocompatibility [3, 20, 21]. Plasma affects biochemical processes of the organism through its active components, consisting of chemically active particles such as ROS and RNS, ultraviolet radiation (UVR), charged particles (positive and negative particles), as well as excited-state and metastable particles. ROS and RNS, primarily O_2^-, OH, O_3, H_2O_2, NO, and NO_2, dominate the biological effects depending on composition and concentration [22]. UVR doses are typically too low to have direct biological effects. Given the lack of effective measurement methods, our knowledge of the impact of excited states and metastable particles is very limited.

Using different discharge parameters – including working gas species, gas flow, and treatment time – a mixture of active agents, characterized by different composition and concentration, can be generated that results in relevant biological responses. A series of cell and animal experiments have shown that the interaction is time- or dose-dependent. While short-time or low-dose plasma treatment can cause rapid sterilization, cell stimulation, promotion of proliferation and migration, as well as repair of damaged DNA, long-time or high-dose plasma treatment results in lethal cell damage (irreversible DNA damage, cell cycle arrest, stop of cell proliferation) and even cell death by apoptosis [6, 7]. Thus, CAP can be utilized for disinfection and wound healing at low dose, and for treating proliferative diseases at high dose.

Effects of CAP on wound healing

Cutaneous wound healing is a complicated process involving various cells and cytokines. It is divided into an inflammatory, a proliferative, and a remodeling phase. Because of the complexity and multiple phases of wound healing, it is easily affected by internal and external disturbances, which may lead to chronic or even nonhealing wounds [7, 23]. Not only do chronic/nonhealing wounds cause medical problems, they also represent a worldwide economic burden. In this context, common conditions include diabetic foot ulcers, pressure sores, cancerous ulcers, and postoperative wound infections.

Cold atmospheric pressure plasma exerts its beneficial effects on chronic/nonhealing wounds through various mechanisms.

Effects of CAP on colonizing microorganisms

Almost all cutaneous wounds are colonized with bacteria. Chronic/nonhealing wounds are characterized by the persistence of bacteria as well as biofilm formation, which both impair wound healing. The most common bacteria are staphylococci, including methicillin-resistant *Staphylococcus (S.) aureus* (MRSA), and anaerobic bacteria; they account for 20 % to 50 % of chronic wound cases [7]. The first step of

treatment is thorough debridement to remove necrotic tissue and exudate, which are conducive to bacterial growth. Simultaneously, systemic or topical antimicrobial agents should be used to eliminate the excessive bacterial burden. However, the use of antimicrobial agents is often limited by hypersensitivity to antibiotics and the increasing development of drug-resistant or multidrug-resistant bacteria. Therefore, novel alternatives that improve chronic wound care are strongly needed. CAP can effectively inactivate broad-spectrum infectious microorganisms within minutes through various mechanisms, without causing allergic skin reactions or resistance to plasma damage [13, 24]. It has been proposed that bacterial inactivation occurs by producing the following: a viable but nonculturable (VBNC) state; peroxidative damage of lipids, proteins, and DNA; programmed cell death in bacteria; direct mechanical cell lysis due to electrostatic pressure [11, 12]. Changes in environmental conditions induced by plasma, such as pH, also lead to the inactivation of biomolecules [25]. Clinical trials have established that CAP treatment reduces the bacterial load and promotes wound healing [3, 26].

Effects on cells involved in wound healing

Cells involved in the wound healing process include keratinocytes, fibroblasts, endothelial cells, and immune cells.

Adequate doses of plasma can promote keratinocyte and fibroblast proliferation and migration, and induce expression of genes relevant to wound healing, such as type I collagen, transforming growth factors (TGF-ß1/2), and alpha-smooth muscle actin (α-SMA) [27]. Studies indicate that plasma can improve vascularization of the wound site. Plasma-mediated ROS, RNS, and fibroblast growth factor-2 (FGF2) release from fibroblasts can promote endotheliocyte migration, proliferation, and tube formation [28, 29]. Moreover, cutaneous oxygen saturation and microcirculation can be enhanced, which improve vascular shear stress contributing to new angiogenesis. New vascular networks and enhanced capillary blood flow increase local oxygen saturation and nutrient supply, thus also promoting wound healing [30, 31]. In addition to the skin, the immune system also plays an essential role in the regeneration process. In vitro studies have indicated that short-term plasma treatment produces some stimulating effects that cause immune cells to proliferate and function actively, thus supporting the antimicrobial defense in removing pathogens. Furthermore, the chronic inflammation of chronic/nonhealing wounds can be transformed into an acute wound healing process.

In short, plasma treatment of wound sites reduces the bacterial load, promotes the action, proliferation, and migration of cells related to wound healing, improves angiogenesis, and increases local microcirculation for sufficient oxygen and nutrient supply. All of the above lead to improved wound healing.

Effects of CAP on skin cancer

Plasma exerts antitumor effects by inhibiting cell metastasis, inducing lethal DNA damage and cell cycle arrest, and causing apoptotic cell death of malignant proliferative cells. The therapeutic effects of plasma are not limited to cultured cancer cells in vitro – such as melanoma, breast, and colorectal cancer cells [8] – but have also been demonstrated in animal models [6, 15, 32, 33]. When irradiated by plasma or injected with PAM, mice with subcutaneously transplanted cancer cells exhibited an extended lifespan. They showed significant inhibition of local tumor growth and reduced tumor volume, without plasma-induced damage to the surrounding normal cells. In addition to direct cytotoxic effects on cancer cells, plasma can also stimulate immune function in vivo, which facilitates tumor regression [34]. It has been reported that plasma treatment may induce immunogenic cell death (ICD) in tumor cells and thus initiate specific systemic antitumor immune responses [35]. Moreover, plasma therapy also exhibits cytotoxic effects against cells that have become resistant to conventional therapies, thus revealing its significant superiority [14]. Plasma can selectively kill malignant cells with no obvious effects on normal cells if treatment duration and dose are appropriate; thus, cancer cells are much more vulnerable to plasma. The mechanisms underlying this selective killing are explained as follows: Cancer cells are characterized by a more active metabolic status, resulting in higher basal ROS and RNS levels and making these cells more susceptible to the oxidative stress added by plasma [14]. It has recently been shown that cancer cells tend to express more aquaporins (AQPs), thereby facilitating ROS transmembrane diffusion. This may be a plausible mechanism for the significant and selective increase in intracellular ROS in cancer cells [36]. Moreover, plasma appears to primarily affect cells in the DNA replication phase, which is the case for a large percentage of cancer cells [15]. In a clinical study, patients with squamous cell carcinoma of the head/neck region showed improvement in cancerous ulcerations and a reduction in tumor proliferation after plasma treatment [37]. The synergistic effects achieved by combining plasma and nanoparticles have demonstrated superior efficacy [16, 38]; this is reflected by increased cell death and enhanced selectivity of plasma in the presence of nanoparticles. In light of the above, skin cancers such as cutaneous squamous cell carcinoma and melanoma respond favorably to plasma and may potentially be suitable indications.

Effects of CAP on psoriasis

Psoriasis is a chronic, relapsing, immune-mediated disease that primarily affects the skin and joints; there has been a worldwide increase in prevalence. To date, there is still no

therapy capable of curing or completely controlling the condition. Key pathogenetic events in psoriatic lesions include aberrant terminal differentiation and hyperproliferation of epidermal keratinocytes, marked inflammatory infiltration, and pathological angiogenesis [39]. The excessive growth of keratinocytes in psoriatic lesions is similar to the characteristic malignant proliferation of tumor cells. The success of plasma therapy in cancer suggests its potential role in the treatment of psoriasis. The assumption that plasma may be a therapeutic option for psoriasis is primarily based on three considerations: First, plasma can be directly irradiated on skin lesions in a manner similar to phototherapy, with both regimens known to induce ROS [40]. In addition, they both inhibit hyperproliferation and induce apoptosis in lesional epidermis resulting in the resolution and clearance of plaques. Cell culture experiments have demonstrated that long-term treatment can induce cell cycle arrest and apoptosis of HaCaT keratinocytes [18, 41]. Besides, downregulation of the expression of surface molecules, such as E-cadherin and epidermal growth factor receptor (EGFR), decreases the stimulatory and proliferative effects of inflammatory cytokines [42]. Secondly, there is evidence supporting the notion that ROS/RNS possess immune-regulatory properties and play a protective role in immune-mediated inflammatory diseases [43]. It has been shown that ROS improve imiquimod-induced psoriasis in a murine model and enhance regulatory T-cell function. In addition, high exogenous levels of NO from plasma have antiproliferative effects and play an important role in the resolution of chronic inflammatory processes [43]. Thirdly, psoriatic skin is characterized by strong AQP3 expression, similar to cancer cells, which promotes transmembrane diffusion of active agents contained in plasma, thus facilitating their selective action [44]. Furthermore, clinical trials have found that plasma treatment inhibits inflammatory infiltration and angiogenesis in psoriatic lesions [19].

Effects of CAP on atopic dermatitis

Atopic dermatitis (AD) is a common inflammatory skin disease, characterized by a chronic relapsing and remitting course and associated with severe pruritus. Various factors are thought to be involved in the pathogenesis, including genetic background, impaired skin barrier, immune system imbalance, and microbial superantigens [45].

The skin of AD patients is either colonized with pathogenic or potentially pathogenic microorganisms, or shows an imbalance in the microbial community, which can trigger or aggravate the disease [45]. Within minutes after plasma treatment, there is a significant reduction in *S. aureus* colonization; other effects include marked improvement in erythema and pruritus [3]. Recently, a mouse model of atopic dermatitis induced by 2,4-dinitrochlorobenzene (DNCB) showed a good therapeutic response to plasma [46]. These promising results favor CAP as an outstanding therapeutic option for AD patients.

Effects of CAP on pruritus

An unpleasant sensation, pruritus is a common symptom associated with various dermatological and systemic diseases that frequently fails to respond to treatment [47]. Plasma treatment has been reported to have beneficial effects on pruritus in AD. It has been suggested that some pruritic dermatoses may be aggravated by the colonization of pathogenic microorganisms. For instance, in AD and prurigo nodularis patients, *S. aureus* can induce increased expression of IL-31, which exacerbates the pruritic reaction mediated by IL-31 receptors [48, 49]. Through its bactericidal effects, plasma thus contributes to reducing the pruritus caused by pathogenic microorganisms [3].

Ultraviolet B (UVB) phototherapy is commonly used to treat pruritus. Although the intensity of UVB radiation and its spectral composition depend on the plasma source, the latter can be designed to increase UVB radiation in order to achieve the desired antipruritic effects. Even though a prospective, randomized controlled clinical trial showed no greater reduction in pruritus following plasma treatment, the marked potential of antipruritic plasma therapy should not be denied. Considering that the study was self-controlled and that possible systemic antipruritic effects of plasma cannot be ruled out, it remains to be seen whether its therapeutic effects are insignificant or not [17].

Others

The bactericidal and fungicidal effects of plasma indicate its possible benefit in bacterial and fungal skin diseases, including folliculitis, impetigo, acne, onychomycosis, and tinea pedis [3]. Given that plasma can inactivate promastigotes of *Leishmania major*, it may also be a potential therapeutic option for cutaneous leishmaniasis. Treatment of Hailey-Hailey disease has also been reported [7].

Conclusions

CAP has been shown to be successful in various medical applications. Using a suitable plasma source, the desired purpose of plasma therapy – bactericidal and fungicidal effects, regulation of cell functions, or induction of apoptosis – can be achieved for various diseases, as shown in Figure 2. As the outermost organ of the body, the skin is amenable to plasma treatment. Plasma can be directly applied to skin lesions, providing immediate therapeutic effects. It also enhances the

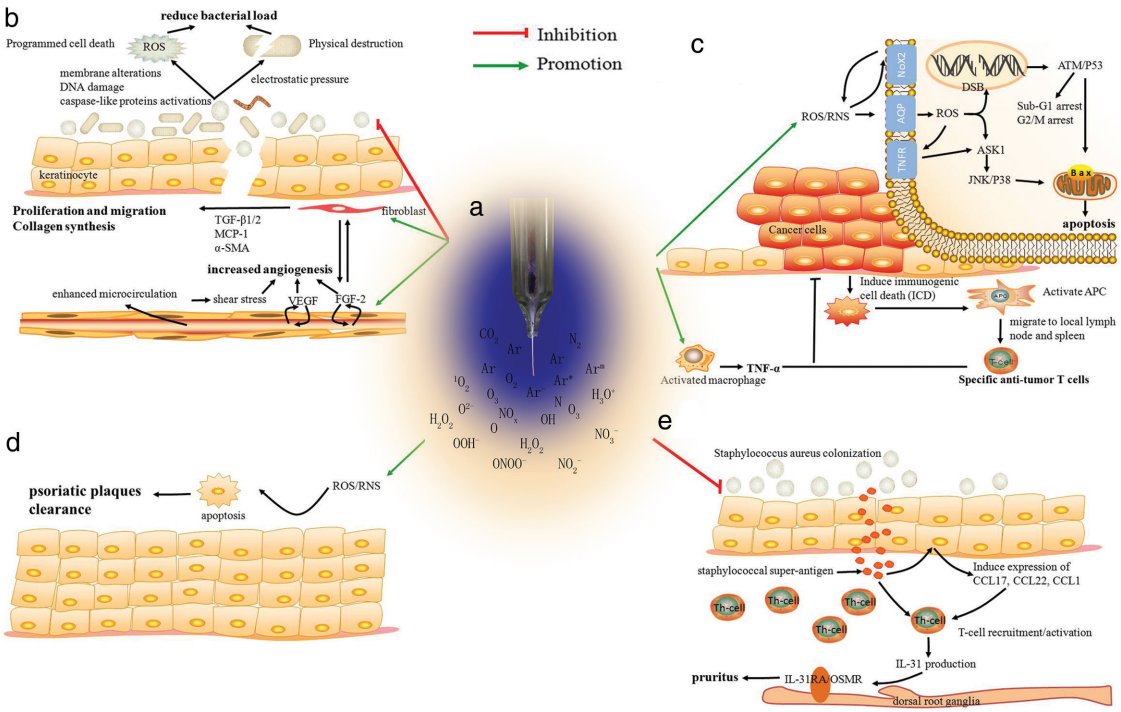

Figure 2 Illustration of the effects of plasma species on various lesions and a general summary of the therapeutic mechanism. Schematic illustration of the APPJ and its active agents (a). Wound healing: the CAP-derived reactive species inactivate pathogenic bacteria, promote fibroblast proliferation and migration, improve angiogenesis, and increase local microcirculation, all of the above resulting in improved wound healing (b). Skin cancer: apart from causing apoptotic cell death, plasma treatment can directly induce lethal DNA damage and cell cycle arrest in malignant proliferative cells. In addition, plasma-induced activation of macrophages and immunogenic cell death (ICD) of tumor cells initiates systemic immune responses (c). Psoriasis: plasma inhibits hyperproliferation and induces apoptosis in psoriatic lesions, resulting in the resolution and clearance of plaques (d). AD and pruritus: bactericidal effects of plasma reduce the pruritic reaction mediated by IL-31 in AD and pruritus patients (e). *Abbr.:* ROS, reactive oxygen species; RNS, reactive nitrogen species; TGF-ß1/2, transforming growth factors; FGF-2, fibroblast growth factor-2; VEGF, vascular endothelial growth factor; α-SMA, alpha smooth muscle actin; AQP, aquaporin; TNFR, tumor necrosis factor receptor; DSB, double-strand break; Nox, NADPH oxidases; ATM, ataxia-telangiectasia mutated; JNK, c-Jun N-terminal kinase; ASK, apoptosis signal-regulating kinase; APC, antigen-presenting cell; TNF-α:tumor necrosis factor alpha; Bax, Bcl-2-associated protein X.

penetration of transcutaneous substances, thereby avoiding the side effects associated with systemic medications. Recently, micron-sized plasma devices have been investigated, which can be utilized inside the body in a manner similar to PAM. Both achieve effects equivalent to CAP. Micron-sized plasma devices can be inserted into lesions or body cavities, where they have been shown to exhibit improved infiltrating capability and to destroy metastatic tumor cells. All of the above shows that plasma treatment holds enormous application and development prospects.

Although there has been considerable progress in the understanding of the biological effects induced by plasma (dominated by ROS and RNS), the precise molecular mechanisms underlying these effects still required further research. In addition, only Mann et al. have described obligatory basic criteria for different CAP sources intended for medical application. Currently, there is no standardized set of technical data for different plasma sources. Various plasma devices from different laboratories use a diverse array of discharge parameters and use active agents of various composition and concentration [50]. This hampers the transferability of results as well as the comparison of research conducted by different groups. In the future, there will be a great need for more controllable therapeutic strategies, larger clinical trials, and confirmation of long-term biological safety.

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