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Translational plasma stomatology: applications of cold atmospheric plasmas in dentistry and their extension

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Abstract: In recent years, translational plasma medicine (TPM), as a novel application area of plasmas, has attracted much attention of experts from both academic and clinical fields. State-of-the-art of the lab-scale research and clinical trials of the cold atmospheric plasmas (CAPs) in the stomatology are reviewed in detail from the direct and indirect applications of the CAPs. Based on the discussions concerning the relationship between the plasma stomatology and the plasma medicine, it is indicated that it would be an important reference for promoting the TPM starting from the fundamental and application studies in the field of dentistry, which is also one of the most three promising application fields of plasma medicine.

1 Introduction

Plasma is defined as the fourth state of matter, and the forms are of great diversity including the nature ones, such as lightning, nebula, Sun's core etc., and the artificial ones, like neon light, confinement fusion, hydrogen bomb, etc. [1]. All of these plasmas can be classified in numerous ways depending on the focused parameters. At atmospheric pressure level, different gas discharge plasmas can be obtained, including thermal plasmas with a gas temperature on the magnitude of 10,000 K, cold plasmas with gas temperatures close to the room temperature, and the warm-plasmas with the moderate gas temperature and energy density. In the field of plasma bio-medical applications, different plasma sources can be employed based on their own features, especially their unique energy density/gas temperature levels. For example, cold plasmas can be used to sterilise the bacteria-contaminated heat-sensitive surfaces of medical instruments with high dosages, and be used for wound healing, cell apoptosis and tissue regeneration with low dosages; warm plasmas can be used for *in vitro* ablation of tissues [2–4]; while for the surface modifications of medical implants or polymer films, different plasmas sources with different energy density levels may be employed, e.g. bio-compatible coatings of medical implants using warm plasmas [5, 6], surface modifications using warm or cold plasmas with appropriate treatment approaches (direct or indirect method) and treatment times. Due to the limit of the paper length, we focus our discussions on the medical applications of cold atmospheric plasmas (CAPs).

The outstanding features of CAPs include the low and controllable gas temperatures and abundant chemically reactive species with high electron energies due to the significant non-equilibrium features of plasmas, flexible operations with vacuum-free instrument configurations, convenient and fast start-up/shut-down and adjustable operating parameters (e.g. chemical composition and flow rate of plasma-working gas, discharge voltage, current or power, action time and distance etc.) with the introduction of automatic control techniques [7, 8]. Morfill and Zimmermann summarised the possible factors which the CAPs possess for their medical applications [9].

As shown in Fig. 1*a* with a helium plasma jet treatment of the biological sample (cell and culture media) as an example, the whole space can be divided into four regions, i.e. the discharge region and the after-glow region in the gas phase, the gas–liquid transition region near the liquid surface, and the plasma-activated liquid region. The originally produced chemically reactive species in the discharge region include helium metastable species (He*, He_2*), helium ions (He^+, He_2^+) etc., if we did not consider the impurities of helium and the back diffusion of the surrounding air with a higher helium flow rate [10]. After the partially ionised gas is issued into the ambient air, the secondary chemically reactive species can be produced resulting from the helium-air reactions, e.g. N_2^+, O_2^+, N^+, O^+. Then, in the vicinity of the liquid surface, due to the evaporation of water, there exist high-concentration water molecules, and thus, H^+, OH, H_3O^+, OH^- are produced. Finally, when these chemically reactive species enter liquid, the reactions in the liquid phase occur producing the long-life (e.g. NO_2^-, NO_3^-, H_2O_2, O_3) and short-life (e.g. NO, -OH, $^1O_2$, $ONOO^-$) species [11–21]. Since the CAPs operate in an open environment with a gas temperature close to the room temperature and the abundant chemically reactive species, on one hand, the etching, deposition or cross-linking may occur when the plasmas act on the surfaces of the bio-medical materials; while on the other hand, the reactive species, especially the reactive oxygen/nitrogen species (RONS) in both the gas and liquid phases after the plasma is produced and acts with cells can possibly result in the cell

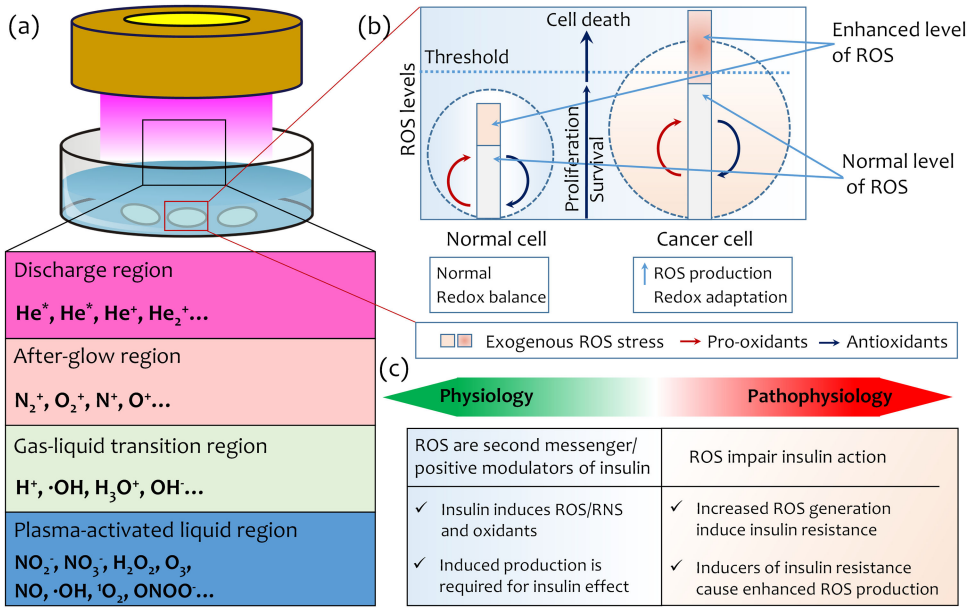

Fig. 1 *Schematics of the helium CAP (cold atmospheric plasma) biological sample (cell and culture media) treatment and its bio-medical effects*
(a) Four sub-regions and the corresponding chemically reactive species, ***(b)*** Selectivity of the normal and cancer cells at an appropriate ROS (reactive oxygen species) concentration level [11, 47], ***(c)*** RONS-based physiology and pathophysiology effects on the insulin actions [11, 48]

signalling, proliferation and differentiation [9, 11]. The detailed explanations of RONS on the living cells will be discussed in detail in Section 2.1.

Translational medicine is an interdisciplinary branch which is regarded as a bridge linking the basic research and clinical application with the 'bench to bedside' and 'bedside to bench' mode (simplified as B to B mode) [22, 23]. In our opinion, the translational plasma medicine (TPM) may be regarded as a branch of the transitional medicine with plasmas as one of the core tools; and the TPM covers two aspects, one aspect is the direct usage of the atmospheric plasmas to treat the medical instruments, bio-medical materials, or air in a space related with medical operations such as the intensive care unit (ICU) and operation rooms, etc.; while another aspect is the direct plasma therapeutic actions on the human bodies including tissues, organs etc. At the present time, there are numerous plasma generators have been used for medical applications which will be discussed in detail in Section 2.2.

Although there are some review papers published previously focusing on the bio-medical materials surface modifications [5, 24, 25] and the plasma therapy [26–36], the purpose of this review is to discuss the applications of the CAPs in dentistry and their possible extensions from the plasma stomatology to the whole TPM. This is because plasma stomatology is one of the most three promising application fields of plasma medicine, i.e. cancer therapy, dermatology and stomatology, at the present time [9, 36, 37]. Thus, we concentrate on the lab- and clinical-scale research of CAPs in stomatology, including both the direct and indirect application aspects, based on an analysis of the relationship between the general plasma medicine and the plasma stomatology. The scope of the literature related with this topic is truly vast and the literatures grow very fast. Although we have tried our best to present a comprehensive review, it is inevitably incomplete, and the readers are encouraged to use the effort here as a starting point only.

2 General aspects of TPM

2.1 Bio-medical effects of the CAPs

During the past decades, the CAPs have been investigated for its promising applications in the pathogenesis of diverse diseases such as neurodegeneration [38], cancer [39–41] and atherosclerosis [42] due to their abundant reactive oxygen species (ROS) and reactive nitrogen species (RNS). The ROS includes superoxide (O_2^-), singlet oxygen ($^1O_2$), hydroxyl radical (·OH), hydrogen peroxide (H_2O_2) etc., which are the products of normal oxygen consuming metabolic process in the body [43]; while the RNS includes nitric oxide (NO), peroxynitrite ($ONOO^-$), nitrite (NO_2^-), nitrate (NO_3^-) etc. Among the preceding RNS, NO found in the late 1980s [44] is an important mediator of the diverse physiologic processes including neurotransmission, regulation of blood pressure, inhibition of platelet aggregation as an effector of the immune responses.

Generally, both ROS and RNS use three main pathways of signalling which result in changes to DNA, proteins and lipids. The free radicals can also modify the enzyme systems involved in the DNA repair and alter the cell death signalling regulated by the key molecules, such as JNK and p38 MAP kinase [45, 46]. The previous results show that it is vital to keep the proper physiological functions of numerous types of cells throughout the body by maintaining the normal cellular ROS and RNS concentrations; that is to say, the concentrations of the RONS determine the shift from their advantageous to detrimental effects, although the concentrations to which this shift happens are generally not known [43]. At low concentrations, the ROS and RNS play an important role as regulatory mediators in signalling processes, whereas at moderate or high concentrations, they are harmful for living organisms by inactivating important cellular molecules. Two examples are presented here: one is the selectivity of the normal and cancer cells illustrated in Fig. 1*b*, in which the basic idea is based on the redox chemotherapeutics which is closely related to the ROS levels [11, 47]; another is the RONS-based physiology and pathophysiology effects on the insulin actions as shown in Fig. 1*c* [11, 48].

In fact, both the antioxidants and free radicals participate in the whole life. Free radicals are not all bad, nor antioxidants are all good. Life is a balance between them. The antioxidants are used to keep the free radicals at normal levels, allowing them to accomplish useful biological functions without too much damages [49]. Thus, on one hand, in order to combat the cytotoxic actions of ROS/RNS, cells are equipped with a large variety of antioxidant defenses, which include enzymes, such as superoxide dismutase (SOD), H_2O_2 scavenging enzymes, hydrophilic radical scavengers and lipophilic enzymes, and are involved in the reduction of the oxidised and cellular enzyme systems [50]. On the other hand, the ROS are thought to be the key agents in all types of antibiotics, some anti-fungal and anti-parasite drugs, as well as for blood coagulation, wound healing and other aspects of dermatology [26, 51, 52]. They play important cell signalling roles when their concentrations are maintained at appropriate cellular concentration levels. The ROS can also modify other oxygen species, proteins or lipids, which is often termed as oxidative stress. In particular, NO

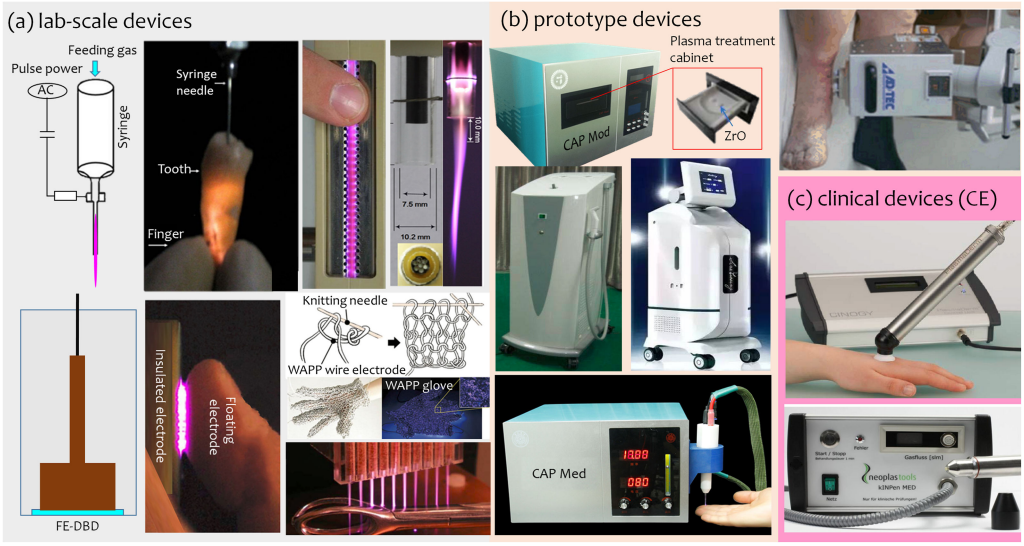

Fig. 2 *Three development stages of the plasma generators used for plasma medicine*
(a) Lab-scale fabricated plasma generators [39, 60, 69, 75–77], ***(b)*** CAP prototypes [34, 71, 78–80], ***(c)*** CE-certificated (Conformite Europeenne) plasma devices [31]

helps to maintain the vascular tone and inhibit the endothelial cell stimulation. It is a regulator of platelet activation and also plays a key physiological role as a second messenger in the cell signalling in neurons and macrophages [53, 54]; while a lack of NO would have significant physiological effects.

Based on the preceding discussions, it is clear that appropriate regulations of ROS and RNS in a CAP system would make the innovative CAPs become a powerful tool in the TPM field for the health care or for the treatment of diseases in future either with the direct irradiation of the CAPs or using the CAPs irradiated media [55, 56].

2.2 Plasma generators used for TPM

Plasma generators used for medical applications can be classified according to their driving frequencies of the power supply ranging from DC to kHz, MHz until GHz, the numbers of the electrodes including the single-electrode discharge, two-electrode discharge with or without the dielectric barrier layers or with the third auxiliary electrode for the discharge transfer from its original breakdown pathway to the third electrode for a stable and large volume discharge, or the geometrical configurations of the electrodes like plate, needle, cylindrical and even flexible electrodes, and so on [57–69]. Except for the lab-scale fabricated generators, there exist some prototypes and clinical devices. The world's first clinical trial with patients is MicroPlaSter (ADTEC Plasma Technology Co. Ltd., Fukuyama, Japan) which is a torch made of a metal cylinder inside which there exist six stainless steel electrodes, and driven by a microwave power supply [70, 71]. Later, some other clinical trials [31, 72] have also been developed. Among of them, two devices, PlasmaDerm® (CINOGY GmbH Duderstadt, Germany) and kINPen MED® (Neoplas Tools GmbH Greifswald, Germany) [31], have received the Conformite Europeenne (CE) certification.

For the specific stomatology applications, most of the plasmas are generated using a needle electrode or used in the form of jet. For example, Sladek *et al.* used a plasma needle to treat the dental cavities which might be the first plasma stomatology trial [73]; Zhang et al used a DBD plasma needle with a funnel-shaped nozzle to inactivate the most important microorganism causing dental caries, *Streptococcus mutans* [74]; Lu used an RC plasma jet to treat the root canal of teeth [75], and developed an comprehensive oral therapeutic apparatus [34]. Some typical but far away from exhaustive devices are depicted in Fig. 2 [31, 34, 39, 60, 69, 71, 75–80]. Although the geometrical configurations, as well as the materials used for the fabrication of the plasma generators are very different, some basic requirements for their medical applications are similar, for example, the controllable and low gas temperature, close to or even lower than the room temperature for some specific applications [80–82], the electrical and biological safety [9, 67, 81], operation flexibility and removability (portability) etc. These basic requirements on the plasma-based medical instruments provide a design guidance for their future development.

3 State-of-the-art of plasma stomatology

3.1 Relationship between plasma stomatology and plasma medicine

Before we review the state-of-the-art of the plasma stomatology, we first give a brief discussion on the relationship between the plasma stomatology and plasma medicine. This is, in our opinion, helpful to understand why plasma stomatology is one of the most three promising application fields of the TPM as stated in Section 1. From the aspect of physiological structure, the oral and maxillofacial region is composed of a variety of tissue structures, including the soft tissue like mucosa and skin, and the hard tissue like bone and teeth. Mostly important, these soft and hard tissues also constitute the tissues and organs in the whole human body. From the aspect of the direct and indirect applications of plasma medicine, there also exist very tight relations between the plasma stomatology and plasma medicine, among which some typical examples can be listed as follows:

(i) There are many kinds of diseases happen in the oral and maxillofacial region. For example, periodontitis and dental caries are the two highest incidence of oral and maxillofacial infectious diseases which happen in the periodontal support structure and tooth structure. The recent studies have reached a consensus that the CAPs have a significant effect on the tooth sterilisation [83]. While on the other hand, the bacterial infections also occur in the systemic diseases, such as the dermatosis or chronic wound infections. Therefore, the CAPs should also play an important role in the treatment of these diseases [33].
(ii) Collagen fibres are the main matrix of dentin, which is an important part of the tooth structure. The research results on the modification of dentins by the CAPs [84] would promote the applications of CAPs in the treatment of the collagen fibre-rich tissues in the human body, such as cornea and tendon.
(iii) The infectious diseases, defection, tumours and trauma happen not only in the oral and maxillofacial region but also in other parts of the human body. The applications of the CAPs to the soft tissue reconstruction within the head and neck regions [85] would provide a guidance for their future applications in the whole human body, such as the tumours in the nasopharynx [86].
(iv) From the aspect of the indirect applications of the CAPs in medicine, on one hand, different types of materials are used in dentistry which include metal, ceramic and implant materials; on

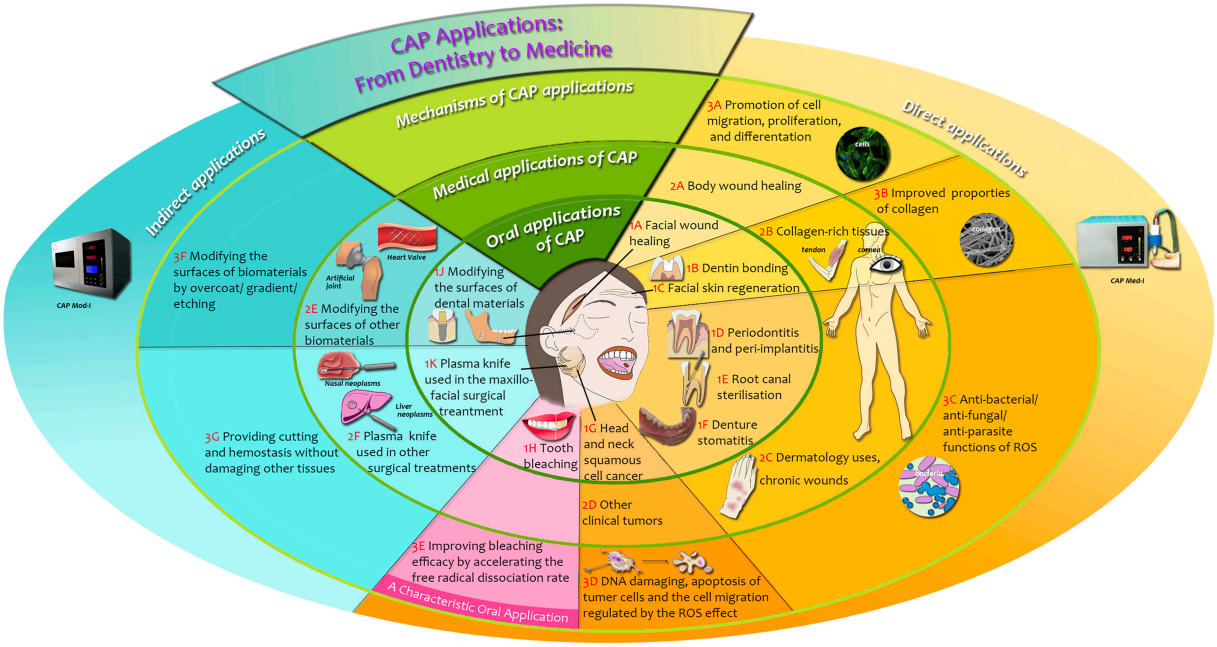

Fig. 3 *Schematic of the CAP applications from dentistry to medicine. (i) The innermost circle indicates the applications of CAPs in dentistry, the middle circle indicates the counterparts of the CAP stomatology applications in the whole human body, and the outermost circle indicates the corresponding CAP treatment mechanisms. (ii) The yellow and blue areas cover the direct and indirect applications of the CAPs, respectively, while the pink area indicates a unique CAP application in dentistry, i.e. the tooth bleaching. (iii) Two prototypes, CAP Med-I and CAP Mod-I, which are developed in the Plasma Health Scientech Group of Tsinghua University of China for the plasma therapy and bio-medical materials modifications, respectively, are also presented*

the other hand, these materials are also used in the orthopaedics and cardiovascular surgery. The applications of CAPs in the bio-medical materials modifications have shown bright prospects, and the plasma-based techniques have been increasingly highlighted in modifying the dental materials in recent years [87, 88].

In addition, the oral and maxillofacial region is an open environment which intrinsically provides an easy way for the plasma treatment and clinical observations. Therefore, the lab- and clinical-scale studies concerning the treatment mechanisms and effects of CAPs on the oral tissue matrix and oral diseases would offer references to those of the CAP medicine, and would strongly promote the applications of the CAPs in the TPM; that is to say, the study of the CAPs in dentistry is a miniature one of plasma medicine, as shown in Fig. 3. Finally, it should be emphasised that, due to the particularity of dentistry, the CAPs also have their specific applications in this field. For example, the dental aesthetics is one of the typical examples. A large number of studies have shown that the CAPs have a significant effect on the tooth whitening [89–91].

3.2 Lab-scale studies in the plasma stomatology

3.2.1 Indirect applications of the CAPs: Compared to the development of new materials, surface modifications of existing materials to make them be more bio-compatible and satisfy the clinical requirements are more likely to be achieved. A variety of methods have been used to modify the biomaterial surfaces, such as laser therapy, chemomechanical instrumentation techniques, ultraviolet irradiation and some cross-linking agents. However, these methods also have their own limitations. Since it is inhibited to destroy the mechanical properties of the material itself and to produce the biological toxic substances after treatment, the possible methods of the surface modifications are to improve the physical and chemical properties of the biomaterial surfaces, for example increasing the surface energy, changing the surface roughness etc. The plasma jet with uniform, stable and high concentrations of chemically reactive particles (e.g. excited atomic, molecular, ionic and radical species) can change the surface properties of the biomaterials, such as wettability, metal adhesion, hardness, chemical inertness, biocompatibility etc. In addition, the plasma technique has also been proven to be a 'clean' approach for materials surface modifications [92, 93]. Therefore, plasma can be used as an ideal method for the surface modifications of biomaterials.

Plasma materials surface modification technologies can be divided into several categories, i.e. plasma overcoat, plasma surface gradient and surface etching [5], as shown in Fig. 4. The plasma treatment for oral materials is mainly manifested in two aspects. The first aspect is the surface modification of the dental materials, mainly related to oral implant materials and adhesive materials [84, 94–96]. The second one is the disinfection of the oral materials, mainly used in the oral medicine materials and restorative materials [97]. In the field of materials surface modification/engineering, plasma is often used as a physical method to improve the surfaces properties of the dental materials, such as the adhesive ability, wettability, biocompatibility and permeability. It is known that good wettability of a dental surface is very important in adhesion improvement of the dental restorations [98]. From the point of view of materialogy, a hydrophilic bonding interface can be used to obtain a better penetration effect, and thus, forming a uniform and complete hybrid layer. This kind of good resin-dentin/enamel sealing effects can not only form the micro-interlocking mechanism but also prevent the generation of the secondary caries. Chen *et al.* reported that the excited argon atoms in an argon CAP were very efficient in the hydrophilicity modifications of the dental composite material surfaces [92]. The similar conclusions were also obtained for the treatment of the ceramic materials, such as yttria stabilised zirconia, while the conventional chemical treatment methods are complex and very possible to produce the biological toxicity. As a safe and clean way to modify the surfaces of the dental materials by grafting to change the functional groups and element compositions of the ceramic surfaces, the wettability and surface energy of the ceramic surfaces were increased, and the bonding strength of the ceramic was also enhanced after the helium APGD or the argon kINPen 09 (INP Greifswald, Germany) treatments [99, 100]. Zheng *et al.* also found that the helium atmospheric pressure dielectric-barrier-discharge plasma treatment not only improved the hydrophilicity of the zirconia material, but also enhanced the biological behaviour of the fibroblasts on the zirconia disks by increasing the expression of the attachment-related genes within 24 h and promoting the cell density during the longer culture periods [101].

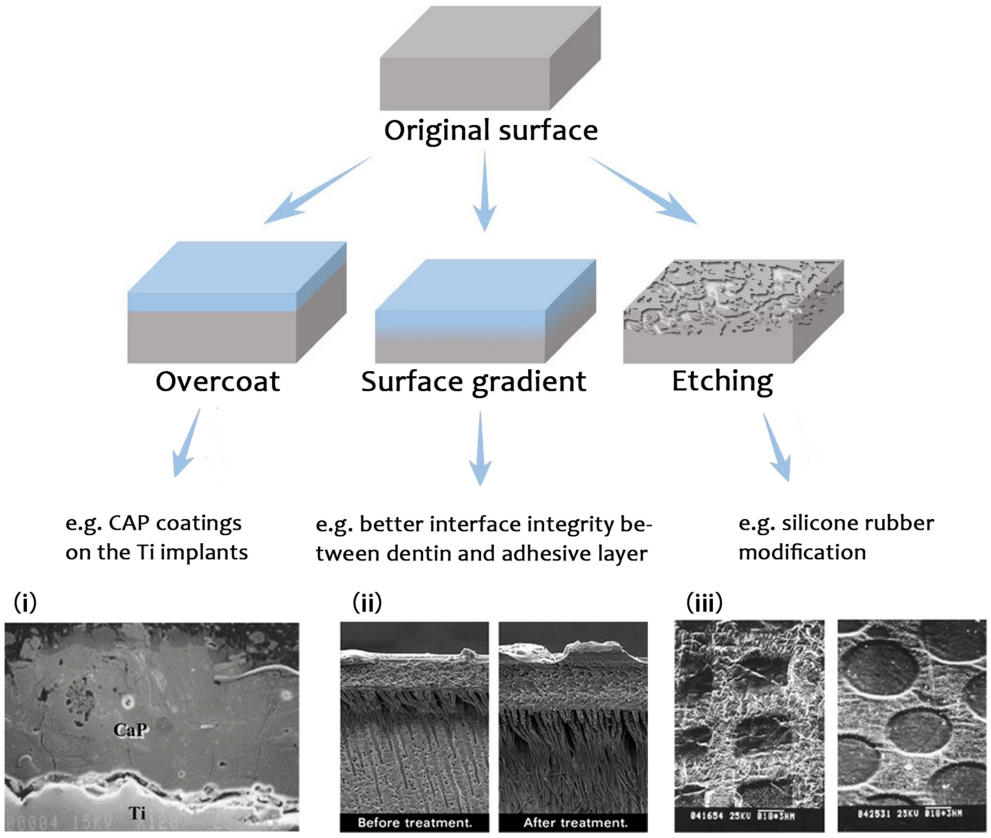

Fig. 4 *Schematics of the plasma bio-medical materials treatment methods*
(a) Overcoat, ***(b)*** Surface gradient, ***(c)*** Etching [94]

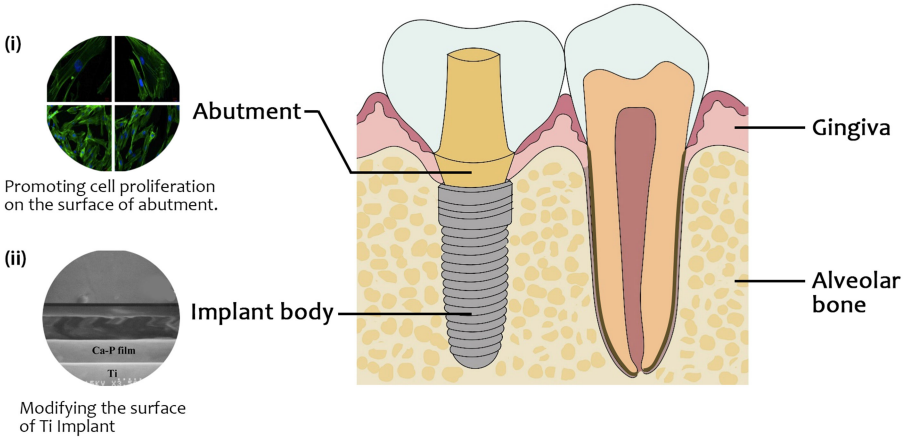

Fig. 5 *Schematic of the relationship between the dental implant structures and the oral environment. The implant body directly contacts the bone tissue (i), while the abutment contacts the soft tissue and gingival [5, 101]*

Dental implantation is an important part of stomatology. An implant contains different structures, as illustrated in Fig. 5: the implant body, the abutment and the upper crown or bridges, as well as the oral environment in which the implant structures are exposed to. For example, the titanium and titanium alloy are widely used as the materials of implant body in dentistry because of their excellent mechanical characteristics. Since they are directly in contact with the bone tissues, it is necessary to maintain a good cell adhesion and to promote the osteoblast proliferation, differentiation and matrix production in the healing phase of the implant. Therefore, in order to achieve a good biological compatibility between different parts of the implant surface and the corresponding host tissues, the surface treatment of the whole implant cannot be completed with only one method for different parts of the implant surface [102]. In this aspect, the atmospheric gas discharge plasma source may be an appropriate tool since it is convenient to achieve different treatment effects by adjusting the chemically reactive species and energy density levels of the plasmas by varying the chemical composition of the plasma-working gas, the power input and driving frequency of the power supply and the geometrical configuration of the plasma generators. This can not only be an effect way to modify the implant surfaces for different host tissues but also obviate the large capital costs for different devices. For example, a rough surface topography of the implant is desired to maximise the area in contact with the bone and allows the contact guidance for the development of osteoblasts at the bone tissue-implant interface [103]. The DC glow discharge nitrogen plasma etching can be employed to treat the implant surface by increasing its surface roughness, which is more conducive to osteoblast adhesion [104]. Similarly, the plasma spraying with ion sputtering can make the titanium implant surface grafting active species and functions, and thus, can enhance the adhesion and differentiation of the osteoblast-like cells [105, 106].

Since the properties of the biomaterials used in other parts of the human body are similar to those of the oral materials, e.g. the heart valves and dental implants are both made of titanium, while

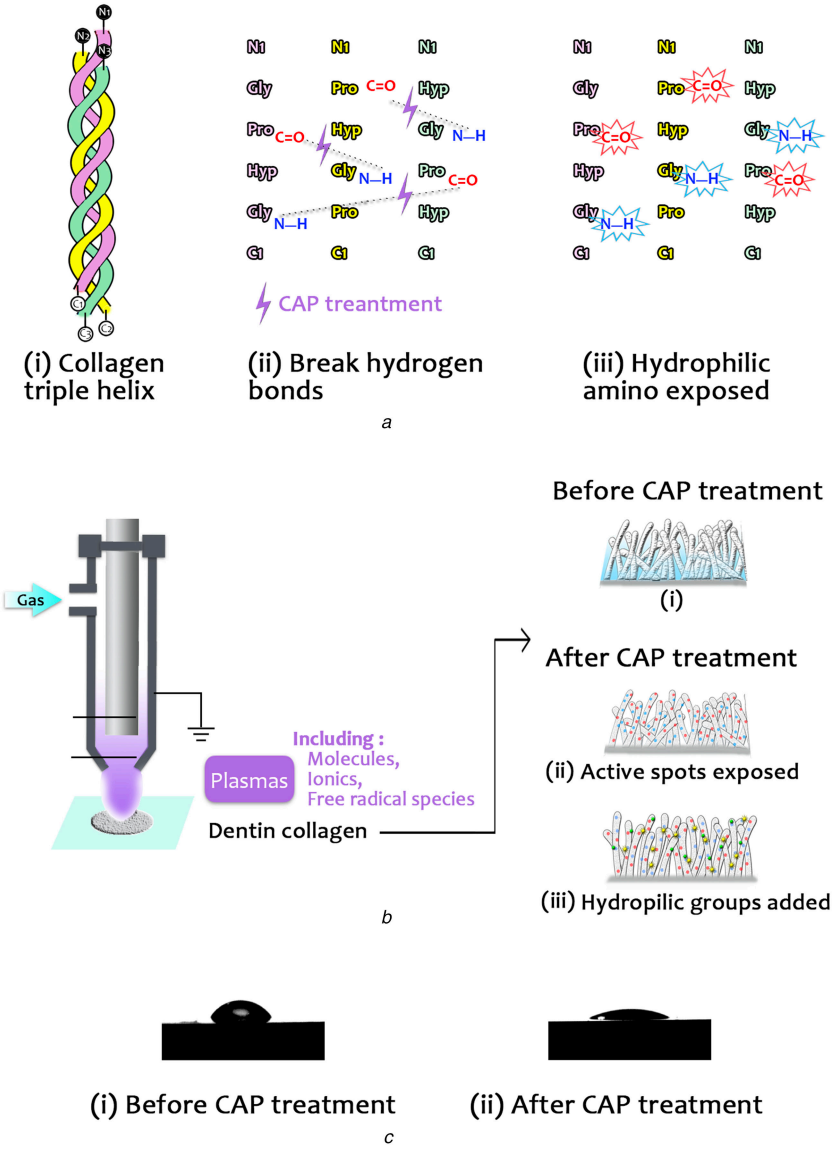

Fig. 6 *Effects of CAP on the demineralized dentin collagen fibres*

(a) Schematic of collagen triple helix structure (i), broken of the hydrogen bonds after the CAP treatment (ii), and exposure of the hydrophilic amino acids inside the collagen helix structure after the CAP treatment, ***(b)*** Plasma treatment to the collagen fibres after the dentin demineralisation (i), production of the active spots after plasma treatment (ii), and grafting of the hydrophilic groups onto the active spots on the surface of the collagen fibres (iii), ***(c)*** Photographs of water drops for the contact angle measurements on the demineralised dentin surfaces before (i) and after (ii) plasma treatment

the bone scaffolds and denture are both made of polymers. Consequently, the materials modification mechanisms and methods for the oral materials can also be extended to those employed in other parts of the whole body. For example, the recent study showed that the helium-oxygen plasma treatment could effectively enhance the transparency of the poly-e-caprolactone nanofibrious scaffolds, and promote the biocompatibility of the scaffolds, which may act as the biological cues for endorsing the ocular surface engineering [107], while the plasma polymer-coated surfaces can be used successfully for the serum-free expansion of the human limbal epithelial cells [108].

3.2.2 Direct applications of the CAPs:

(i) Treatment of collagen fibres

The chemical and mechanical properties of the tooth surfaces are important for the success and sustainability in the restorative dentistry. The effects of CAPs on the modifications of the tooth tissues have been widely used in the dentin bonding. In dentistry, the resin restoration is very important, but also very difficult, for achieving a long durability of the dentin bonding. It is well known that the bonding strength of dentin is mainly determined by the hybrid layer. Therefore, the mechanism of the plasma treatment to the dentin bonding is the modifications of the collagen fibre. As shown in Fig. 6*a*, the collagen fibre is formed by a triple helix micro-structure, which has a single interstrand N–H(Gly) ···O=C(Xaa) hydrogen bond per triplet. Due to the abundant chemically reactive species existing in the jet region of the CAP plasmas, the hydrogen bonds can be broken after the CAP treatment, accompanied with the exposure of the hydrophilic amino acids; and then, these amino acids, with N–H(Gly) or O = C(Xaa) working as the active spots, can interact with the chemically reactive species provided by the plasmas to form the hydrophilic group; and consequently, the hydrophilicity of the plasma treated collagen fibres are improved significantly, as illustrated in Figs. 6*b* and *c*. For the first time, Ritts *et al.* applied the argon DC glow discharge to the field of dentin bonding, and indicated that the plasma treatment of the peripheral dentin surface for up to 100 s resulted in an increase in the immediate bonding strength [84]. Chen *et al.* found that the non-thermal atmospheric plasma brush (fabricated by Nanova, Inc., Columbia, MO, USA) treatment of the dentin surface could enhance the hydrophilicity and permeability of the dentin, and thus, could improve the immediate dentin bonding strength [109].

Except for the improvement of the bonding strength of the dentin after the CAP treatment, recent studies suggested the possibility of the CAPs application for the acceleration of the wound closure. Compared with other conventional methods, the

helium pulsed DC plasma jet treatment technique could lead to the acceleration of the tissue repair processes without adverse effects on the normal tissues [110]. For example, Matrigel *et al.* found that the 10 T1/2 cells cultured *in vitro* on the microsecond pulsed (μsp) and nanosecond pulsed (nsp) DBD plasmas treated type I collagen showed an increased expression of the adhesion proteins and activation of the survival pathways. These results indicated that the CAP modification of the extracellular matrices could influence the cellular behaviours, and consequently, could accelerate the chondrogenesis and endochondral ossification [111]. In addition, although the type I collagen fibres are the major collagen fibres in dentin, they are widely distributed in various organs of the human body, e.g., the collagen fibres in skin, cornea and tendon. Thus, the effect of plasma treatment on the type I collagen in dentin would also have important reference for the modifications of the collagen fibres existing in other organs of the body.

(ii) Bactericidal effects

The bacterial infection has long been recognised as the primary etiologic factor in the development of caries, pulp and periapical lesions and periodontitis [112]. The biofilms can be built up on the teeth surfaces, and can lead to the dental caries, which is a localised destruction of the tooth tissues by the bacterial fermentation of the dietary carbohydrates, if they are not removed regularly. In dentistry, the purpose of the root canal treatment is to eliminate the infections of the root canal system. On one hand, the endodontic infection is generally a polymicrobial infection of the dental root canal system; on the other hand, it is very difficult to achieve a complete elimination of the biofilms from the root canals using traditional methods, such as the mechanical debridement, chemical irrigation, and ultrasound, because of the complexity of the root canal system [113]. Many publications in recent years have demonstrated that the CAPs have outstanding sterilisation effects on the microorganisms. The possible reasons of the sterilisation ability of the CAPs on bacteria might be that the plasma can destroy the cell membrane, genetic materials and/or protein of the bacterial. The *in vitro* study by Pan *et al.* showed that the single-electrode non-thermal DBD plasma jet treatment could rupture the bacteria membrane and destroy the structure of the biofilm [114]. Yang *et al.* reported the bactericidal effect of a DC argon plasma brush on *Streptococcus mutans* and *Lactobacillus acidophilus*, which are the major pathogens in the dental caries [115]. Sun *et al.* [116] compared the bactericidal efficacy of the plasma treatment of the root canal infected with *Enterococcus faecalis* biofilms *in vitro* using two different types of CAPs (glow discharge and DBD). It was found that the DBD plasma had a better bactericidal effect on the bacteria than that using the glow discharge plasma, which may be due to the higher concentrations of the excited argon atoms in the DBD discharges. Du *et al.* [117] evaluated the *in vitro* antibacterial activity of CAP on the *E. faecalis* biofilms, which is attributed to the persistent endodontic infections [118]. Their experimental results showed that the 5-min treatment with the CAP could kill the majority of the bacteria in the *E. faecalis* biofilms and the infected root canals, and no differences were found between the bacterial survival in a complex root canal system and that in a simple straight canal [117]. Simoncelli *et al.* reported a thorough investigation of different plasma (direct and indirect treatment)-based endodontic procedures assisted by the handheld coaxial DBD plasma gun with which the *E. faecalis* was selected as the bacterial strain, showed that the direct exposure under dry conditions could lead to a bacterial load mean reduction of 4.1 [119]. All these studies indicated a very bright promising application of the CAPs for the treatment of the complex structures like the root canal system. In addition, an acceptable mechanical safety can be achieved with no significant influences on the microhardness and roughness of the root canal dentin after plasma treatment [83].

Periodontitis and peri-implantitis are two kinds of inflammatory diseases affecting the surrounding tissues of the natural teeth and the implant. The bacterial biofilms also play a key role during the onset and progression of the periodontitis and peri-implantitis lesions [120]. Therefore, the biofilm removal is also important for the treatment of the periodontitis and peri-implantitis. Pierdzioch *et al.* [121] used the CAP in combination with scaling and root scaling (SRP) for the treatment of the root surfaces infected with *Streptococcus mitis*. Their results showed that the bactericidal efficacy of the SRP+CAP treatment is significantly higher than that of the SRP treatment alone. Rupf *et al.* [122] found that the CAP jet treatment together with application of the air-water spray could disinfect and remove the *in situ* formed biofilms from the microstrctured titanium. Idlibi *et al.* [123] presented the similar results and found that the efficacy of CAP treatment was dependent on the plasma treatment time and the discharge power. Shi *et al.* [124] built an experimental peri-implantitis in the position of the fourth mandibular premolars in a beagle dog. The experimental results showed that, compared with the conventional techniques (e.g. the elevated flaps, curetted plaque, calculus and granulation tissue, irrigated with 0.2% chlorhexidine digluconate and sterile saline solution), the combination of the conventional techniques and the CAP could lead to a higher bone level, significantly decreased detection of bacteria (*Porphyromonas gingivalis* and *Tannerella for sythia*), and a significant improvement in the clinical examination.

Due to the intrinsic features of the CAPs, the sterilisation effects of the CAPs can also be extended to kill different pathogenic microorganisms for the treatment of various diseases, while with no obvious damages to the normal tissue structures. Maisch *et al.* demonstrated that the CAP was able to very efficiently kill the bacteria on an intact skin surface using an *ex vivo* porcine skin model [125]. Daeschlein *et al.* showed that the argon CAP had a potential to limit the multidrug-resistant bacteria microbial colonisation [126]. Moreover, Brun *et al.* showed that a short exposure to the CAP could be regarded as an efficient and rapid ocular disinfectant for the bacteria and fungi without significant damages to the ocular cells and tissues [127].

(iii) Anticancer effects

Except for the tooth-tissue-related diseases, dentistry also covers the oral and maxillofacial tumours. The head and neck squamous cell cancer and the oral malignant tumour are the most common types of cancers. Owing to the abundant blood supply in the maxillofacial region, the malignant tumour in the oral and maxillofacial region is prone to metastasize. Therefore, the average 5-year survival rate of these diseases is about 50% [128]. In recent years, effects of different types of CAPs on the cancer cells have attracted much attention of the researchers. Although the mechanisms of the CAP treatment on the cancer cells are not clear yet, it has been speculated that the anticancer effects of the plasmas, e.g. the DNA damage and the apoptosis of the tumour cells, may be due to the RONS effects [129–131]. The generated short-lived chemically reactive species in the CAPs can induce a cytotoxic insult in the cancer cells, decrease the tumour cell viability in a dose (time)-dependent manner, and induce the ROS-, JNK- and caspase-independent mechanisms of the cell death in the special cell lines [132]. Welz *et al.* proved that a surface-micro-discharging (SMD) plasma device was effective against the head and neck cancer cell lines, and confirmed that the SMD plasma technology was definitely a promising new approach for the cancer treatment [133].

Except for the killing of the oral and maxillofacial tumours, the CAPs have also been applied to the anticancer treatment of other tumours. For example, Binenbaum *et al.* demonstrated the efficacy of RF plasma treatment against melanoma *in vitro* and *in vivo* [134]. Brulle *et al*. also showed that the DBD plasma treatment to different types of cancerous cells could lead to the inhibition of the cell growth and cell cycle arrest [135, 136]. These results indicate that the CAPs may be employed as a novel tool for the treatment of different kinds of solid tumours in future.

(iv) Wound healing

CAP also plays an important role in wound healing of the inflammatory gingival tissues surrounding the teeth. Except for the previously mentioned plasma sterilisation effects with the control of the chronic inflammation, recent studies have proved that the plasma treatment with an appropriate time and energy density level can increase the cellular activities, which is responsible for the wound healing [33]. For example, Kwon *et al.* reported that the mRNA expressions of the growth factors in the human gingival fibroblasts could be increased after the air DBD plasma jet

treatment which is helpful in the gingival wound healing process [137]. In addition to the periodontal inflammatory tissue, the wound healing in the dentistry also includes the skin injury during operation. Owing to the invasion of malignant tumour to the normal tissues and organs, maxillofacial tumours often cause the tissue defects after operation. This not only affects the normal physiological function of the patients but also causes great trauma in the psychology of the patients. Various studies have presented a stimulation of the growth and migration of fibroblasts after plasma treatment [138, 139]. Similar to the inflammatory disease and injury in the oral and maxillary area, there is also a process of wound healing in the surgical injured skin. Lendeckel *et al.* showed that the argon kINPen 08 plasma treatment could influence the cellular adaptation of the upper airway epithelial S9 cells which are helpful for the improvement of the wound healing [140]. Here, it should be emphasised that the CAP treatment is a double-edged sword for the tissue healing; that is to say, the effects of cell regulation are very different with different dosages of the plasma treatment. It is reported that the non-thermal DBD plasma treatment could induce the dose-dependent promotion or inhibition of the endothelial cell mediated angiogenesis [141].

(v) Plasma aesthetics

Aesthetics is also an important part of stomatology, including both the dental aesthetics and facial aesthetics. Facial aesthetics mainly refers to the regeneration of the facial skin. Plasma skin regeneration is a novel type of skin rejuvenation technology developed over the recent years. Unlike lasers, which rely on the principle of selective photothermolysis by delivering heat to the specific targets in the skin, plasma technology delivers heat energy directly to the tissues upon contact without reliance on skin chromophores [142]. The epidermis regenerated after the CAP treatment shows a smoother surface profile than the adjacent untreated tissues [143].

Tooth blenching is an important aspect of the dental aesthetics and is also a common request of patients. The use of conventional light might result in an increase in the temperature of tooth, and thus, cause the thermal damages to the health of the tooth tissues. The application of the CAPs in the tooth whitening can greatly reduce the damages of the enamel surface and improve the whitening effect. This is a unique application of the CAPs in dentistry in contrast to the plasma medicine. Nam *et al.* investigated the efficacy of tooth bleaching using the helium DBD plasma jet combined with 15% carbamide peroxide ($CH_6N_2O_3$) and 5.4% H_2O_2, and compared with that for the case of conventional light sources. They found that with the aid of CAP, a higher capability for the effective tooth bleaching could be obtained under a lower concentration of H_2O_2 without the thermal damages [89, 144]. The morphological results of the teeth using the scanning electron microscope (SEM) after plasma treatment showed that the plasma treatment did not alter the mineral compositions of the teeth [90]. Lee *et al.* also found that the helium DBD plasma jet could enhance the tooth bleaching effect of the hydrogen peroxide, and the possible reasons might be the removal of the tooth surface proteins and the increase of the production of ·OH [145]. In addition, the CAP is also effective on the intracoronal tooth bleaching in blood stained human teeth [146].

3.3 Clinical applications in the plasma stomatology

Based on the unique and outstanding features of the CAPs and the lab-scale studies on their bio-medical effects, it is anticipated that there is a bright prospect for the clinical applications of different types of CAPs covering not only the sterilisation of heat-sensitive medical instruments and surface modifications of bio-medical materials and implants but also diseases therapy.

Clinically, the bacterial and fungal infections are the most common diseases inside the oral cavity. The therapy is routinely carried out using the anti-fungal agents. However, the drug therapy is usually limited to time, and the long-term use of drugs may lead to the drug resistance. The battle against the antibiotic-resistant bacteria is one of the greatest challenges in medicine in the twenty-first century, and new approaches are required to solve this problem. Both the laboratory research and the clinical trials on animals prove that the argon kINPen 09 (CE certification No. 609.003.1) jet and the round metal electrodes volume DBD plasma (INP Greifswald, Germany) are effective in against a wide range of pathogens including *Candida albicans* [147, 148]. It was reported that the argon/oxygen single-electrode plasma jet seemed to be a promising and convenient strategy for preventing the early adherence of *C. albicans* on the acrylic resins, which would be greatly benefit for the potential dental applications [149]. As drug therapy is usually limited to the time in which signs of infection are present, the tissue-tolerable plasma jet is an effective treatment tool for the denture stomatitis patients. Preissner *et al.* reported that the erythema surface was reduced significantly and extensively compared with the control groups between 2 and 6 weeks during the antifungal therapy. This indicated that the CAPs might be helpful for reducing the usage of the antifungal agents [150]. Recently, a plasma jet was employed in dermatology for the antimicrobial treatment of the skin, especially in the case of the chronic wounds. Isbary *et al.* reported that the application of MicroPlaSter plasma torch resulted in a significant reduction in pain and clearance of bacterial carriage, allowing antibiotics and analgesics to be ceased [151]. A clinic study with the analysis of 38 chronic infected wounds in 36 patients treated by the cold atmospheric argon plasmas showed a significant reduction of the bacterial load in the treated wounds, regardless of the type of bacteria [71]. To the chronic leg ulcers, the plasma treatment also achieved good clinical effects. Ulrich *et al.* indicated that the immediate antimicrobial effects of the argon kINPenMed prototype source were almost comparable to the octenidine without any signs of cytotoxicity [152, 153].

In the aspect of wound healing, the results *in vivo* showed that the main roles of the CAPs were to promote the formation of microcirculation and sterilisation. It is proved by experiments on animals that the plasma was safe and effective for the treatment of tissues. Hartwig *et al.* demonstrated that all patients who suffered the complete wound repair in terms of the absence of tendon exposure were observed within a mean treatment time of 10.1 weeks in average, while no undesirable side effects were observed, and no inflammation or infection occurred [85].

The plasma-based skin regeneration technique is mainly applied to the skin epidermis and dermis; while the dermis consists of the collagen and the elastin fibres. A plasma action may include the removal of the old photo-damaged epidermal cells at the surface of the skin, and the promotion of the growth of the collagen below the skin [154]. Therefore, we can speculate that the skin regeneration technology with plasma treatment is beneficial to the anti-aging and modifications of the collagens. This has the potential to be applied to the collagen-rich tissues, such as the cornea and tendons.

Owing to the abundant facial nerve and blood supply in the maxillofacial region, the traditional surgical treatment may lead to the injury of the facial nerve and multiple minor bleedings, which may affect the physiological function of the patients. The low-temperature, tripolar plasma knife has become an electrosurgical device designed to provide cutting and haemostasis within a single instrument. The incidence of the facial nerve paresis is also lower than that of the conventional operative techniques [86]. In addition, the intraoperative haemorrhage caused by the unclear visual field is one of the important reasons related with the intraoperative facial nerve injury. Gillespie *et al.* used a plasma knife with a tripolar electrocautery in the head and neck surgery, and an outer plasma bipole on the tip rapidly alternated between a cutting and a coagulation setting to produce a haemostatic cut [155]. Therefore, the plasma knife nerve dissection seems to be a safe and effective alternative to the conventional methods. Nowadays, the plasma knife has become a safe and effective tool in a number of gynecologic, urologic, and general surgical procedures [156]. For example, the plasma knife is a useful and safe device in tonsillectomy, which reduces the intraoperative blood loss and provides a fast tonsillectomy with acceptable morbidity [157].

In conclusion, on one hand, the tissues and organs in the oral and maxillofacial region include the teeth, alveolar bone and gingival soft tissues inside the oral, and the skin and glands in the maxillofacial region, and the basic components of these organisations, such as the cells in the glands, the collagen in the

skin and dentin, the maxillofacial tumour, the minerals in the teeth and alveolar bone, can also be found inside the corresponding tissues and organs in the whole human body. On the other hand, although most of the plasma applications in stomatology is still at the laboratory level at the present time, more and more studies on animals and clinical pilots indicate that there would be a promising prospect in the oral clinical medicine. Thus, we can conclude that the plasma treatment methods in the oral and maxillofacial region can very possibly be extended to the treatment of other clinical diseases as a more general clinical technique in the near future.

4 Discussions on the key issues in the development of TPM

Since the requirements on the characteristics of the CAP generators, as well as the crucial physicochemical processes which influence the plasma treatment effects, corresponding to specific applications may be very different from the plasma stomatology to the whole plasma medicine field, it is indispensable to spare no effort to collaborate to investigate the bio-medical effects and the corresponding mechanisms in a synergy environment including not only the physicists, chemists and biologists but also the medical scientists and clinical experts [67]. In this section, some common issues including the key scientific issues and the core technology issues related with the development of TPM are discussed as follows:

(1) Design of the plasma generation system: optimal design of the CAP devices is undoubtedly the foundation of the scientific research and technology development in the field of plasma medicine. On one hand, there exist significant influences of the geometrical configuration and electrode materials of the plasma generator, chemical compositions of the working gas and driving frequency of the power supply on the discharge characteristics. On the other hand, the operating safety of the plasma generators and the stability and repeatability of the physical and chemical properties of the discharges are of great importance from the point of view of clinical applications.

(2) Selection of the working media: Since the CAPs operate in an open environment, not only the plasma-working gas but also the ambient environment have significant impacts on the gas discharge processes and the key plasma parameters which are vital for the clinical applications. For instance, addition of 1 ppm water vapour into the working gas (helium) could cause the disruptive changes in the compositions of the chemically reactive species [158], while the ambient environment can also effectively regulate the plasma jet length and reactive species in the plasma jet region [159, 160].

(3) Understanding and regulating to the interfacial processes: The plasma production and materials treatment processes involve complicated multi-face processes. These interfaces include the plasma-electrode/suspended solid wall/cell membrane interface, plasma-ambient gas interface, and plasma–liquid interface. Scientific research and regulation on the physical and chemical processes occurring at these interfaces are crucial for maintaining a steady gas discharge with desired parameters, and for obtaining excellent plasma treatment results. With plasma stomatology as an example in this review, the saliva would have effects on the actual applications. Although, to our knowledge, there seems no research published on the plasma–saliva interactions [12], the studies on the plasma–liquid interactions, which is one of the very active research aspects in the field of plasma science and technology, would promote the specific studies about the plasma–saliva interactions in the plasma stomatology.

(4) Regulation of the key plasma parameters: The precise and effective control of the key plasma parameters are of great importance for the plasma clinical applications. Under the atmospheric pressure condition, the frequent elastic and inelastic collision processes inside the plasma system itself, as well as between the main plasma stream and the surroundings, have significant influences on the discharge mode, stability, and the key plasma parameters. Thus, the quasi-independent regulations of the gas temperature, electron temperature and concentrations of the chemically reactive species in plasmas become very important, and simultaneously, relatively difficult.

(5) Achievement and regulation of the plasma bio-medical effects: In the field of plasma medicine, different bio-medical effects after plasma treatment can be obtained which depend not only upon the unique features of plasmas, e.g. the energy density levels of the discharges, the kinds and concentration levels of the chemically reactive species, but also the properties of the treated materials, as well as the plasma action approaches, e.g. materials treatment in the discharge region or in the jet region.

(6) Evaluation of the plasma dosage and establishment of the standard: up to now, the so-called plasma dosage acting on the living biomaterials is usually evaluated based on the discharge parameters (e.g. voltage, current, power, flow rate etc.) and/or the treatment parameters (e.g. plasma treatment distance, time etc.). However, since numerous factors may influence the characteristics and the action effects of plasmas as discussed above, it is indispensable to establish a standard including a complete set of method and parameters for evaluating the plasma dosage and performance which is independent of the specific plasma generation method from the point of view of clinical applications. Recently, the first German DIN-specification 91315 named as 'General requirements for medical plasma sources' was published in June of 2014, and was demonstrated using the plasma device kINPen® Med in 2016 [161]. This paves a new way for the standardisation of the medicine-related CAP devices and the corresponding operation procedures.

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