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Original scientific paper

Application of non-equilibrium plasmas in medicine

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Abstract: The potential of plasma applications medicine, the connections to nanotechnologies and the results obtained by our group are reviewed. A special issue in plasma medicine is the development of the plasma sources that would achieve non-equilibrium at atmospheric pressure in an atmospheric gas mixture with no or only marginal heating of the gas, and with desired properties and mechanisms that may be controlled. Our studies have shown that control of radicals or chemically active products of the discharge, such as ROS (reactive oxygen species) and/or NO, may be used to control the growth of the seeds. Simultaneously, a specially designed plasma needle and other sources were shown to be efficient to sterilize not only colonies of bacteria but also planktonic samples (microorganisms protected by water) or bio films. Finally, it was shown that a plasma might induce differentiation of stem cells. Non-equilibrium plasmas may be used in detection of different specific markers in medicine. For example proton transfer mass spectroscopy may be employed in the detection of volatile organic compounds without their dissociation and thus as a technique for instantaneous measurement of the presence of markers for numerous diseases.

Keywords: low temperature plasmas; plasma technologies; sterilization; functionalization; stem cells.

INTRODUCTION

This paper provides a survey of current plasma medical research/applications in the context of nanotechnologies, in particular, some of the research that was realized in our laboratory.

Low temperature, non-thermal or more precisely non-equilibrium plasmas have shown extraordinary range of applications and range of targets that may be

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treated. Some of the applications, such as plasma etching for integrated circuit production plasma sources of light, gas lasers and deposition of thin films, have already shaped the existing civilization,[1–5] some on the other hand promise to make a similar impact in the future. Medical applications are at the forefront of future technologies associated with low temperature plasmas and the most active front of present day research.[6–9]

Non-thermal plasmas are being widely used in nano-technological and biomedical applications due to several distinctive properties.[1,2,10,11] The key feature is that it is possible to achieve dramatic changes of surface chemistry at low temperatures. Most of the generator power is absorbed by the electrons in the discharge, which then become hot, typically of the order of 10000 K or more, while, at the same time, ions and neutral molecules maintain room temperature, or close to it. The gas composition, the electron energy distribution function and the cross sections for the dominant interactions between electrons and the background gas particles dictate the production of huge amounts of chemically active species. If the gas composition is chosen properly and if the applied fields are designed efficiently and appropriately, the effects required by a certain application may be achieved while simultaneously fulfilling the criterion of maintaining a low temperature of the background gas.[12]

For the nano-technological applications, the main advantage is the anisotropic ion bombardment of surfaces (Fig. 1). Namely, sheaths are formed near surfaces due to the difference in particle masses. These high field regions conveniently accelerate ions, often with no collisions, to allow (nearly) normal incidence impacts at the surfaces, converting the potential energy in the sheath into kinetic energy at the surface.[14] A normal incidence angle is a crucial factor for contact holes to be obtained and interconnects with high aspect ratios. It is thought that the technology of combined photolithography and plasma etching is the most widely employed nanotechnology (belonging to the top down group) ever since the barrier in miniaturization of 200 nm was broken. The present day resolution of 32 nm in manufacture and aspect ratios of up to 20 (and much smaller dimensions achieved in laboratories) truly challenge even the bottom up technologies.

Furthermore, ion impacts on the sample surface are isolated because the time between impacts onto an area of ≈1 nm^2 is about 10^{-3} s. This should be compared to the time of 10^{-12} s required for the energy of a single impact to dissipate to the background heat. In unison, a single ion impact dissipates several hundreds of eV locally, which is sufficient to make a significant albeit localized modification of the surface. A typical flux of 10^{17} ions cm^{-2} s^{-1}, on average, dissipates power densities of the order of 1 W cm^{-2}. Thus, significant local and superficial changes of the surface structure are obtained while the overall temperature is not

increased significantly. The point here is that the peak power is sufficiently high to break chemical bonds easily and to perform functionalization of the surface.

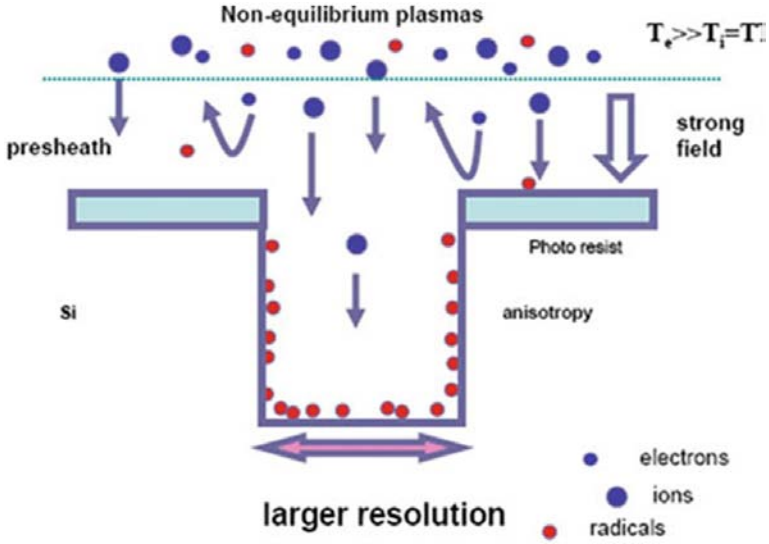

Fig. 1. Schematics of anisotropic plasma etching in non-equilibrium plasmas. The bulk of the plasma produces low energy ions and somewhat higher energy electrons that produce new ions and chemically active radicals. The sheath slows down the electrons and accelerates the ions, thus giving them energies of the order of several 100 eV. Hence, when they hit the surface they do so at a right angle and they facilitate anisotropic etching without sidewall undercutting. Electrons hit the surface with an almost isotropic distribution. The combined effect of the ions and radicals is much greater than the sum of the individual effects of the two species.[13]

It is also well known that the individual effects of ions and neutral chemically active species can be dramatically increased[13] when they both impact surfaces. This kind of synergy of the plasma agents is another crucial property in nano-technological applications.

Neutral, chemically active radicals are created in large numbers by electron-impact dissociation in molecular gas plasmas. It could easily be assumed that the surface flux of reactive particles (density) scales with pressure but gas phase collisions and slower diffusion as well as three body processes, which may change the chemistry entirely, have to be taken into consideration. The higher fluxes of active particles are one of the main arguments for atmospheric pressure non-thermal plasma sources over the low-pressure sources. This was one of the driving forces towards replacing low-pressure plasmas with atmospheric pressure/gas composition plasmas, together with the increased simplicity and decreased cost of atmospheric pressure systems. Thus, the needs of modern nano-technologies gave impetus for the development of more efficient and varied at-

mospheric pressure sources of low temperature plasmas. With the opportunity for such a development, a new front easily opened - that of medical applications.

Another advantage of atmospheric pressure, non-equilibrium plasmas is, of course, the fact that most biomedical systems cannot be subjected to vacuum. Moreover, for most biomedical applications, the temperature of the background gas should not exceed 42 °C, when cell death due to the overheating is induced. Hence, the ultimate conditions for biomedical applications would be not to overheat the sample but rather to induce subtle and selective cell and tissue responses to the plasma-generated chemicals and other species. Similar to nano-technological applications, but probably even more important is the understanding of the synergetic effects of the plasma agents, namely ions, electrons, electric fields and currents, light, neutrals, radicals and metastables. It can be concluded that common goals together with a common need for a localized synergistic effect of several agents drive the applications in both nanotechnologies and plasma medicine. Sometimes plasma medical effects that may be observed over a larger area are in essence due to very localized and specific effects that are fully in tune with nanotechnologies, their criteria and needs.

A BRIEF HISTORY OF PLASMA MEDICINE AND ITS CURRENT STATUS

The history of atmospheric pressure plasma applications in medicine can be divided into several periods. The first generation of plasma devices dating back to 1900 were those when heat was mainly used for tissue removal (plasma cutter). This period was followed by the second generation (since 1970) where thermal plasma energy was used for the surface treatment of tissues (argon plasma coagulator). In addition, there were numerous associated applications such as those using dielectric barrier discharges (DBD) for water purification, electrostatic precipitators to cleanse the air in hospitals and plasma activated hydrogen peroxide as sterilizer. At the same time, low-pressure plasmas were efficiently used in the early 1990s to sterilize equipment.[15] The third generation commenced in the late 1990s when plasmas were used, mainly at atmospheric pressures, for surface treatment with charged particles, reactive UV photons and electric fields.

The first commercial plasma devices date back to the beginning of the 20th century and those were aimed at surgery.[16] At present, there are numerous surgical devices but one has to be aware of the distinction between whether a plasma is just a conducting medium between an electrode and the treated tissue while the effect is due to thermal heating that is the result of the passage of the current or whether the surgical effects are due to plasma-created particles and their interaction with the fields and surface. One of the most successful devices associated with surgical interventions are plasma related devices for stopping bleeding, both by thermal effects and/or by plasma influence on the surface.

These devices include the endoscopic usage of APC (argon plasma coagulation) developed in 1995.[17]

Another front of medical applications that proved to be very successful expanded from low pressures[15] to atmospheric pressures in the late 90s. Very efficient sterilization of bacteria *Escherichia coli* was demonstrated by Laroussi in 1999 using a helium DBD.[18] This line of studies was pursued either directly in Petri dishes[19] or in planktonic samples (in liquid)[20] or even in biofilms.[21] More importantly, sterilization by a plasma was shown to be one of the benefits in the treatment of wounds.[22]

In addition to sterilization, plasmas were shown to benefit proliferation of new cells and the removal of scar tissue.[23] Thus, numerous wounds were treated including burns and chronic wounds, such as diabetic foot.[23] One of the recent applications of microwave plasma applications in dermatology for the treatment of chronic wounds is the application of the plasma torch MicroPlaSter®.[22]

In vitro treatment of cancer cells was demonstrated in 2007 using a floating electrode dielectric barrier discharge (FE-DBD) plasma.[24]. With this device, it was possible to induce programmed death of cells, so-called apoptosis. The Plasma acts directly on the cell without poisoning the solution in which they are located, even when the cells are covered with a medium.

The ion source of a proton transfer mass spectrometer (PTR-MS) operates using a non-thermal plasma. PTR-MS, compared to other analyzing devices, is more sensitive and can detect volatile organic compounds (VOC) down to parts per trillion in real time sampling. Breath sampling and analysis can provide data on VOC for the early stage detection of various diseases, such as breast and lung cancer, diabetes *etc*. Breath is a very complex mixture of various organic compounds.[25] For lung cancer, VOC-31 (m/z = 31), tentatively protonated formaldehyde, and VOC-43 (m/z = 43), tentatively a fragment of protonated 2-propanol, were found at significantly higher concentrations in the breath of cancer patients than in the breath of the control group.[26] One of the biomarkers for diabetes is acetone[27] and its higher concentration in breath, as well as the dynamics of its removal can be an indicator for the disease.

EXPERIMENTAL SETUP AND PROCEDURE

The main reason for the application of plasmas in medicine is that they can replace old conventional procedures in surgery and wound sterilization. Another important feature is the simplicity and low production cost of these plasma devices. Various plasma sources are used in plasma medicine, such as plasma jets, plasma needle, APC and FE-DBD (Fig. 2). Most of the plasma devices have low working gas temperatures because of the great non-equilibrium between the energies of the electrons and heavy particles. This feature is crucial for treatment without damaging the sample. In order to ignite and maintain a discharge at atmospheric

pressure, a noble gas is often used (usually helium or argon). The main role of the noble gas is to lower the breakdown voltage and with its flow, the treated area is also cooled. The complex chemistry and reactions in a plasma produce a unique mixture of particles, for instance atomic species, radicals, UV photons and electrons, important for the efficiency of the treatment of a biological sample. In order to produce higher concentration of the reactive species, a mixture of the noble and a molecular gas, usually oxygen, can be used.

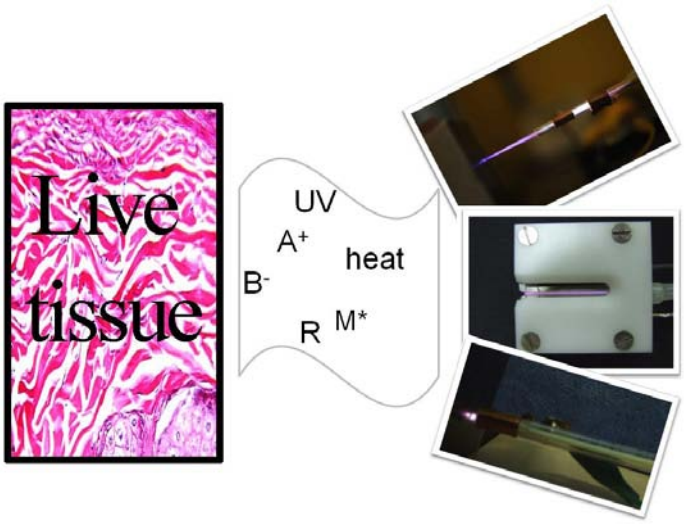

Fig. 2. Photographs of several atmospheric plasma devices that are used in our laboratory for biomedical applications. From the top, a plasma jet, a micro atmospheric pressure plasma jet and a plasma needle are shown.

In our laboratory, low-pressure plasma reactors are accessible that have been used mainly for the treatment of surfaces (textile, polymers, graphene, silicon dioxide surfaces, *etc*.). Atmospheric pressure non-equilibrium plasmas that are available include plasma needle, micro atmospheric pressure plasma jet, plasma jet (operating in the plasma bullet mode), corona and dielectric barrier discharge.

Our principal plasma device that was used to date in the studies of plasma medicine is the plasma needle, which was first applied for the treatment of mammalian cells reported in 2003.[28] The operating power was low and the frequency of the driving current was 13.56 MHz in atmosphere of helium. The plasma needle can be used for the treatment of small areas covered by cells. The plasma needle at higher power kills cells, usually causing necrosis, but at smaller powers either apoptosis may be induced or cells could be just separated.

This plasma device was shown to be suitable for bacteria sterilization[20] of bacteria colonies, planktonic samples and bio films. In addition, this source was

shown to be able to destroy cancer cells, affect but to a much lesser degree human stem cells and even cause differentiation of the stem cells.[29]

DIAGNOSTICS OF PLASMAS

In order to determine the pertinent plasma properties and optimize the desired effects, we use several diagnostic methods. In principle, the basic electrical properties are determined by probes (including derivative probes for higher frequencies that have been calibrated to determine the powers delivered to a plasma of less than 1 W). Optical emission spectroscopy is applied with a limited range of interesting effects that may be covered unless time resolved measurements are made. Spatial profiles of emission recorded by an ultra fast ICCD are employed to determine the time dependent anatomy of the discharge. Finally, a mass analyzer with triple differential pumping is employed, which enables sample ions or radicals from atmospheric pressure discharges to be sampled.[30,31]

MECHANISMS

The interactions between a plasma and cells are hard to investigate due to the complexity of both systems. A plasma is a cocktail of active agents (radicals, UV light, heat, ions, electric fields, energetic particles, *etc*.) with strong synergetic effects. The proper diagnostics and optimization of plasma treatment is of vital importance. On the other hand, the biological samples being treated have a complex sub-structure of their own, so plasma usually targets and affects several of them if not all. The character and the selectivity of the interaction are determined by the plasma properties and the structure of the bio-sample. For example, UV light can easily penetrate and reach DNA introducing single and double strand breaks (directly and/or by creating radicals in the vicinity of the DNA).[32] In the case of bacteria, the DNA is in the nucleoid and is circular while the eukaryotic cells have their DNA better protected in the nucleus. The same intensity of UV light exposure can lead to the destruction of bacteria without long-term effects on the eukaryotic cell, which is just one of the examples of the selectivity mechanism. Other examples worth discussing can be drawn from the differences in the surface to volume ratios, the structure of cell walls, the existence of cell enzymes, *etc*.[33] Bacteria have a higher surface to volume ratio meaning that the same dose of plasma exposure can be sufficient for deactivation while no negative effects to surrounding tissue is caused. The cell wall is usually directly exposed to the plasma treatment. Due to ion bombardment (or to the strong electric fields), pores are being created in the cell wall.[34] Through these pores, the cell can exchange its content with the surrounding. The cell content can leak out and cause cell stress and eventually cell death, as often happens. Bacteria cell wall is made of polysaccharides. Eukaryotic cells have walls made of phospholipids. Exposed to the plasma, lipid peroxidation process occurs. In the process of peroxidation of polysaccharides and phospholipids, the presence of water is important as well as

the composition of the media surrounding the cells and the ions play a catalytic role. One of the products of the lipid peroxidation process of the cell wall is the malondialdehyde. Formed at the cell wall by the plasma, malondialdehyde can be transported to the vicinity of DNA where it can introduce DNA mutation.[35] All this shows the indirect effects of the plasma as well as the complexity of the cell reactions. The enzymes are also able to regulate the stress dealt to the cell. They also regulate the cell radical levels, which on the other hand are massively produced by the plasma. The importance of reactive oxygen and nitrogen species through cell redox processes is evidently crucial but not sufficiently understood.[36] Some of the reactive oxygen species are listed in Table I.[37] The balance between the free radicals and the antioxidants is necessary for proper cell functioning. The conclusion is general and valid for plant cells also.[37]

TABLE I. Reactive oxygen species, ROS[37]

Radicals	Non-radicals
Superoxide, $O_2^{\bullet -}$	H_2O_2
Hydroxyl, $OH^{\bullet}$	Hypobromous acid, HOBr
Hydroperoxyl, $HO_2^{\bullet}$ (protonated superoxide)	Hypochlorous acid, HOCl
Carbonate, $CO_2^{\bullet -}$	Ozone, O_3
Peroxyl, $RO_2^{\bullet}$	Singlet oxygen ($O_2{}^1\Delta_g$)
Alkoxyl, $RO^{\bullet}$	Organic peroxides, ROOH
Carbon dioxide radical, $CO_2^{\bullet -}$	Peroxynitrite, ONOO
Singlet $O_2{}^1\Sigma_g^+$	Peroxynitrate, O_2NOO

PARALLELS WITH PLASMA NANOTECHNOLOGIES

Plasmas have been used in top down plasma technologies for many years, especially through synergistic process of plasma etching that is presently massively used in production with resolutions of 32 nm. Several plasma applications in nanotechnology may be associated with medicine. These include coating of biocompatible thin films, functionalization of surfaces to allow binding of bactericidal nanoparticles of TiO_2 or silver, thus allowing the development of germ free clothes for surgeons and other medical personnel.[38–45]

Furthermore, a more direct parallel lies in the fact that most plasma medical processes are very local over areas that are small parts of a cell and thus compatible with nano-dimensions. Besides the plasma needle and micro atmospheric pressure plasma jet, the capillary microplasmas used for nanostructuring have similar potentials for biomedical applications.[46,47] In a similar way, non-equilibrium plasmas are used to achieve thermodynamically unlikely structures/effects and in the same way surfaces are bombarded by a cocktail of ions and neutrals, electrons, chemically active radicals and are subjected to the effects of local fields. Finally, the need for atmospheric pressure for plasma medicine is also a

motivating factor for the development of cheaper nano-technologies not employing expensive vacuum procedures. Thus, the development of plasma medicine may be associated with the advances in non-equilibrium plasmas for micro (nano) electronics that have occurred over the past two decades.

CONCLUSIONS

Recent advances in plasma medical applications have left very little doubt that this application will be the main driving force for the future developments of non-equilibrium collisional plasmas. The main trick in achieving the non-equilibrium operation and no gas heating is the control of the electron multiplication. For this purpose, inhomogeneous fields (corona), dielectric barrier, RF and pulsed operation and breakdown in rare gas flow may be employed.

Plasma medicine is a new and fast developing field of both medicine and plasma physics, introduced in the last decade. The non-thermal atmospheric pressure plasmas were recently used for the treatment of diverse thermo sensitive biological samples.

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И З В О Д

ПРИМЕНА НЕРАВНОТЕЖНЕ ПЛАЗМЕ У МЕДИЦИНИ

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У овом раду дат је преглед примене плазме у медицини, повезаност са нанотехнологијама и резултате на овом пољу које је постигла наша група. Посебан проблем у плазма медицини је развој извора плазме који би радили у неравнотежним условима на атмосферском притиску и у смеши гасова каква је у атмосфери уз занемарљиво грејање гаса и са жељеним карактеристикама које се могу подешавати по жељи. Наша истраживања су показала да се контрола присуства радикала и других хемијски активних честица као што су реактивне кисеоничне честице (ROS) и/или NO, може користити за контролу клијања семенки. У исто време је доказано за посебно конструисану плазма иглу да може ефикасно да стерилише не само колоније бактерија већ и планктонске узорке (микроорганизме заштићене водом) па и биофилмове. На крају, ми смо показали да плазма може да индукује диференцијацију матичних ћелија. Неравнотежна плазма се може користити за детекцију разних специфичних маркера у медицини. На пример масена спектроскопија на бази измене протона може да се користи за детекцију испаривих органских једињења без њихове дисоцијације и на тај начин се може оставрити тренутна детекција маркера за бројне болести из даха.

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