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Biomaterial and Medical Applications of Plasma-Induced Chemical Processes in Liquid
プラズマ誘起液中化学プロセスを用いたプラズマ医療

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It has been demonstrated that atmospheric plasma jets can be used for non-conventional plasma processing that involves liquids. A system with a single HV electrode for atmospheric plasma jet (LF plasmajet) has been developed. LF plasmajet are energetic enough to generate highly reactive species but their gas temperatures remain low, nature of which enables attractive applications. It was found that plasma produced active species in gas is transported into liquid to induce chemical reactions. In this paper, applications of attractive reaction field in liquid to biomaterial and medicine have been examined

1. Plasma-induced chemical processes in liquid

Based on unique characteristics of low gas temperature atmospheric pressure plasmas, novel plasma processes in liquid have been developed [1]. Various species (ions, electrons, radicals UV, and so on) generated in plasmas are used to obtain desired chemical reactions in liquid. For that purpose, LF (Lower Frequency) plasmajet was developed. This is a simple system with a dielectric tube through which He gas flows and a single electrode to which LF high-voltage pulses (~10kV, ~10kHz) are applied [2,3]. Due to its low gas temperature, as shown in Fig.1, this type of jets is desirable for plasma processing in liquid. Diameters of 10 microns ~ 30 mm can be controlled, depending on applications.

For worthful applications of attractive plasma-induced chemical processes in liquid, many collaborative projects have been conducted with researchers of different areas (biomaterial, molecular biology, dentistry, medicine, physical chemistry, protein chemistry).

2. Applications to Biomaterial

Plasma reduction of cations in the liquid has been used for the synthesis of nanosized particle for biosensor with core-shell structure[4]. When LF plasmajet was exposed to the surface of a auric acid solution with some dispersant, the color of the solution became pinkish red. This suggests that Au nanoparticles were synthesized and dispersed in the colloidal solution.

Y_2O_3 nanophosphors for near infrared flourescence bioimaging, acidic durability was durability improved by plasma treatment [5].

Polymeric micelles formed in water have been extensively studied as a candidate of drug delivery system. With the plasma exposure to the solution, stabilization of micellar structures was achieved by the core-polymerization [6].

Biomaterial specialized for plasma treatment was developed [7]. Several methods have been developed for the improvement of biocompatibility of the surfaces of bio-devices made of various plastics. By plasma exposure, where experiments were done not in gas, immobilization of a plasma susceptible polymer to the polypropylene substrate was improved.

3.Applications to Medical

For the medical application to control the infection diseases, inactivation of bacteria in liquid is distinctly important. Considering human body, some reaction should be induced inside body fluid. In gas, bacteria can be directly exposed to plasma and it is not so difficult to inactivate. When bacteria is in liquid, water works as the scavenger of plasma and it generally becomes difficult to inactivate.

Successful bactericidal activity was found to be achieved if the solution is sufficiently acidic[8,9]. It

Fig.1 LF plasmajet exhausted to a finger without burning.

is interesting to note that there is a critical pH value of about 4.7 for the bactericidal effects, below which the bacteria are efficiently inactivated and above which they are hardly affected by the plasma application. When the plasmas were exposed to *E.coli* suspensions at pH 5.2, 4.7, 4.2 and 3.7, D values were found to be 120, 58, 35 and 13 second respectively, under some weaker plasma conditions, as shown in Fig.2. D value of about 2 second was achieved with usual plasma condition. In the present, plasmas indirectly applied to the solution can bring same results and it is confirmed that neither heat nor ozone from the plasma is the cause of bacterial inactivation. This suggests the importance of highly reactive species generated inside the solution via plasma–air–liquid interactions for the bactericidal effects.

It has been also found that the presence of superoxide anion radicals (O_2^-•) in water and the air is essential. The critical pH value may be associated with pKa of the dissociation equilibrium between O_2^-• and hydroperoxy radicals (HOO•), which is known to be approximately 4.8. This means that O_2^-• can be changed into HOO•, which have much stronger bactericidal activity, in lower pH. Here, long-lived O_2^-• has so much longer half lifetime in water than other reactive oxygen species that the reduced pH method would effective not only on surface of solution but in volume.

This reduced pH method have been applied to root canal therapy in dentistry. Many kinds of oral pathogens were confirmed to be inactivated efficiently with lower pH [10]. Disinfection experiments inside a root canal of human extracted teeth have been successively achieved. Recently, collaborative research projects of its medical application to bedsore healing, wound healing, surgical site infection have been started.

Another medical application of hemostasis (stop bleeding) is started. In animal experiment, bleedings from femoral vein and resected body organ (liver, kidney) were confirmed to be stopped.

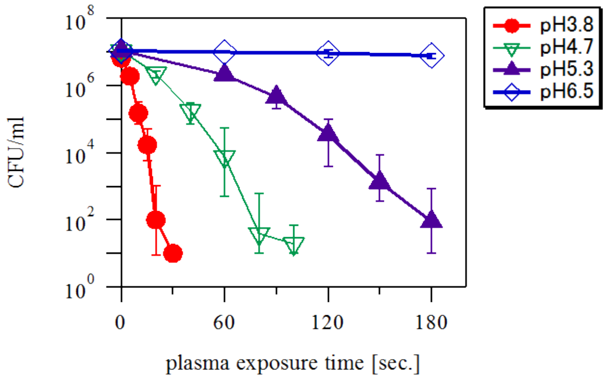

Fig.2 Bacterial inactivation assay in various pH solutions as functions of plasma exposure time.

Blood coagulation was observed just upon the surface layer of blood bleeding. Unlike the reduced pH method, direct plasma exposure to blood seems to be essential for hemostasis. This means short-lived species generated are essential and the reaction process is different respectively. By contrast with commercially available APC (Argon Plasma Coagulator), which uses thermocoagulation by thermal argon gas plasma, cold plasmas like LF plasmajet would bring much less tissue damage in depth. LF plasmajet for endoscope have been developed for gastrointestinal tract surgery.

4. Elementary Processes of Reactions

Many attractive experimental results have been achieved with the plasma-induced chemical process in liquid. To clarify the elementary processes, plasma produced active species was measured and their reaction to biomacromolecules was evaluated.

The formatio of radicals in solution have been studied from ESR (Electron Spin Resonance) and MS (Mass Spectroscopy). Concerning the reduced pH method, it was found that air ions of O_2^-• in gas is brought to the water solution to produce O_2^-• in liquid. Bacteria in water can be inactivated by the combination with the reduced pH method and free radicals from non-contact plasma.

To clarify the affect of active species to cell, which consists of polysaccharide, amino acid, protein and lipid etc., plasma treated biomacromolecules in liquid were analyzed [11].

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