2nd Asia-Pacific Conference on Plasma Physics, 12-17,11.2018, Kanazawa, Japan

Challenge to the systematization of the biological interaction by plasmas

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A development of non-thermal atmospheric pressure plasmas has been driving the innovation in the plasma bio field including plasma medicine and plasma agriculture. There are two methods to approach to the plasma bio field. One is the direct exposure of plasma to organism. Another method is the indirect one, where the plasma is exposed to the liquid in advance and then the plasma activated liquid is injected to the organism. In both cases, there are significant effects on the organism.

Recently, plasma activated medium (PAM) has been proposed as an indirect plasma exposure technique. It enabled to cause the selective death of various kinds of cancer cells, which is an epoch-making topics in the field. Through in vitro and in vivo experiments with the plasma irradiation of culture medium, we have developed novel and innovative medical uses including selective induction of apoptosis to destroy cancer cells. It is of crucial importance to develop a fundamental theory to explain the control of eukaryotic cellular behavior by integrating information from plasma science, medical science, molecular biology, biochemistry, and cell biology particularly to enhance understanding of the universal molecular mechanisms underlying cell death.

In this article, we introduce our approaches to make the theoretical systematization of hierarchical and integrated seamless understanding of the connections between plasma and higher organisms[1)].

Firstly, there have been many atmospheric pressure plasma sources for bio applications. The experiments for bio and medicine have been done by try and error methods. For example, the main plasma parameters are equipment parameters, such as the gas, the power, the irradiation time and the distance between the plasma and the substance. It is necessary to characterize the plasma by using internal parameters, such as the electron density, the electron temperature, the gas temperature and the density of neutral and ion species for establishing the plasma bio science. Additionally, the spatio-temporal distribution measurement of these parameters is so important to clarify the mechanism of gas reactions. We have developed the ultrahigh density atmospheric pressure plasma source of electron densities beyond $10^{16}cm^{-3}$ and investigated the spatial distribution of behaviors of the electron density, the electron temperature and the densities of atomic species of H, N, O and OH by using the laser Thomson scattering, the vacuum ultraviolet absorption spectroscopy and the laser induced fluorescence, respectively.

Secondary, these species are irradiated on the liquid and/or organisms. The clarification of interactions of reactive species and/or charged particles with such the liquid and organism is a key issue to establish the plasma bio science. Particularly, the ROS/RNS species play important roles to stimulate cells and living tissues. We have investigated behaviors of ROS/RNS such as short live species of OH and long live species of NO_2^- and NO_3^- together with H_2O_2 by using Electron Spin Resonance (ESR) and UV absorption spectroscopy. The reaction kinetics of these chemical element in PAM were much different from those in the PBS and a pure water. The ESR potentially enabled us to study the effects of plasma on organism in a real time. Furthermore, in the case of intracellular molecular changes, various kinds of biomolecular methods have been used for clarifying the dynamic mechanism. We have developed the multiplex Coherent Anti-Stokes Raman Scattering (CARS). The CARS enabled us to analyze the dynamic change of chemical structures inside the cells treated by the PAM.

Recently, behaviors of lipid bilayer membrane of cell with the irradiation of plasma have been focused on because effects of plasma induced reaction on cells are firstly brought about on the lipid bilayer membrane. The dynamics behaviors of the artificial ones irradiated by the plasma were measured in the liquid at a real time by the rapid speed atomic force microscopy (AFM)

On the basis of these results, the comprehensive understanding of interactions of plasmas with the liquid and cells will be preceded and integrated.

Thirdly, the most important studies *in vivo* toward the preclinical test are much different from those *in vitro*. We have been studying the effects pf PAM on mice. As a result, the PAM has been exhibiting a strong antitumor effects on glioblastoma, ovarian, gastric, pancreatic cancers in mice. Furthermore, the high selectivity of killing cancer cells against normal cells has been confirmed *in vitro*. It was found that the PAM attacked cancer specific signaling structures. The differences of sensitivities to PAMs are not only used for selective killing of cancer cells but also selecting desirable cells (or eliminating undesirable cells). We showed that PAM was used to eliminate undifferentiated human induced pluripotent stem cells. Recently, we have proposed a new medical liquid irradiated by the plasma, which is PAL (plasma activated lactate). The PAL exhibited better results than the PAM. The PAL has more simple chemical elements. It enabled us to determine the specific organic structures working on the selectively killing cancer cells.

Although the clinical test with PAM and PAL are a big challenge, to establish the plasma bio science and to demonstrate safety tests are going on.

1) H. Tanaka et al., “State of the art in medical applica”, Rev. Mod. Plasma Phys (o6 July, 2017) 1:3, DOI: 10. 1007/s41614-0004