5th Asia-Pacific Conference on Plasma Physics, 26 Sept-1Oct, 2021, Remote e-conference

Low-temperature plasma-activated solutions and metabolic modification

Kenji Ishkawa[1], Hiromasa Tanaka[1], Hiroaki Kajiyama[1], Shinya Toyokuni[1], Masaaki Mizuno[1], and Masaru Hori[1]

[1] Center for low-temperature plasma sciences, Nagoya University

e-mail: ishikawa.kenji@nagoya-u.jp

Non-equilibrium atmospheric pressure plasma (NEAPP) can be used in medical devices for treatments at near body temperature [1]. This capability enables the irradiation of liquids with NEAPP or low-temperature plasma. The NEAPP-irradiated solutions were shown to induce apoptotic cell death in exposed cells and tissues and they exhibit selective cytotoxicity toward cancer cells as opposed to normal cells [2]. Presently, we have proposed a usage of Ringer's lactate solution. This known as plasma-activated lactate (PAL) has been for early clinical applications [3].

To date, a synergism of H_2O_2 and NO_2^- generated in the plasma-treated solutions demonstrated the selective cytotoxicity [4,5]. The study of the molecular mechanisms of cell death in the NEAPP-irradiated solutions revealed downregulation of cell survival and proliferation signaling networks with respect to phosphoinositide 3-kinase (PI3K)/AKT signal transduction pathway [6], and upregulation of gene expression of stress-inducible signaling pathways such as growth arrest and DNA-damage-inducible protein (GADD45α) signaling, commonly responsible for reactive oxygen species (ROS) stress [7].

In recent studies of the PAL, it is suggested that the non-oxidative stress and the other plasma-produced substance promote regulated cell death selectively toward cancer cells. Metabolomic profiles of intracellular metabolites were characterized in dying cells treated with Ringer's lactate solution or PAL. It was revealed that PAL inhibits cellular energy production in glycolysis and tricarboxylic acid (TCA) cycle and activates specific metabolic pathways during cell degeneration, while glutathione levels were indicative of non-oxidative stress or death-associated reductive stress [8]. Cellular oxygen consumption rate and extracellular acidification rate of the PAL-treated cells were measured by extracellular flux analyzer. This result showed that the PAL inhibited glycolysis and TCA cycle and increased intracellular ROS regardless of extracellular ROS [9]. From these, the other substances are responsible for some of the plasma-induced cell deaths [6].

Cancer cells are intrinsically rich in catalytic Fe(II) for proliferation and autophagy supports the proliferation under starvation or metabolic stress due that its catabolic process facilitates in lysosome by digestion of cytoplasmic components. This lysosomal autophagic process is regulated by nitric oxide (NO). By, suppressing the homeostatic antioxidant actions eventually by PAL, catalytic Fe(II) executes a regulated cell death called as ferroptosis by accumulation of lipid peroxidation and increase in ROS level. NO is a potential regulator of ferroptosis [10].

Importantly, it is necessary of hierarchical systematic analyses for solving the mechanisms of the low-temperature plasma-induced effects in biology [11,12]. Diagnostics in gas-phase has revealed quantitatively the ROS generation. However, interactions among interfaces of multiphases have not still solved. In particular, NEAPP generates the various reactive species and the organic substances, which have not been completely identified. To find this species, we hope that the interactions between plasma and liquid can be analyzed by newly developed, sophisticated diagnostic methods.

Acknowledgements

The authors would like to thank profs. K. Nakamura, Y. Okazaki, M. Kato, T. Kondo, K. Imoto, T. Tsutsumi, C. Miron N. Britun, H. Kondo, M. Sekine, for fruitful discussion and all the lab members for technical assistances. This study was partly supported by JSPS-KAKENHI nos. 19H05462, 17H02805, 20H00142, 21H04451; the joint usage/research program of the center for low-temperature plasma sciences, Nagoya University; and the plasma-bio consortium, National Institute of Natural Sciences.

References

[1] H. Tanaka, K. Ishikawa, *et al.*, Modern Reviews on Plasma Physics **1**, 3 (2017).
[2] F. Utsumi, H. Kajiyama, *et al*. PLoS One **6**, e81576 (2014).
[3] H. Tanaka, K. Nakamura, *et al*., Scientific Reports **6**, 36282 (2016).
[4] N. Kurake, H. Tanaka, *et al*., Archives of Biochemistry and Biophysics **605**, 102 (2016).
[5] N. Kurake, K. Ishikawa, *et al*., Archives of Biochemistry and Biophysics **662**, 83 (2019).
[6] H. Tanaka, M. Mizuno, *et al.,* Plasma Medicine **2**, 207 (2014).
[7] H. Tanaka, M. Mizuno, *et al.*, Scientific Reports **9**, 13657 (2019).
[8] K. Ishikawa, Y. Hosoi, *et al*., Archives of Biochemistry and Biophysics **688**, 108414 (2020).
[9] H. Tanaka, S. Maeda, *et al*., Plasma Processes and Polymers, 2100056 (2021).
[10] L. Jiang, H. Zheng, *et al*., Redox Biology **43**, 101989 (2021).
[11] K. Takeda, K. Ishikawa, *et al*., J. Phys. D: Appl. Phys. **50**, 195202 (2017).
[12] K. Ishikawa, M. Hori, *et al*., *Physical and chemical basis of nonthermal plasma*, In *Plasma Medical Science*, ed. by S. Toyokuni et al. (Academic Press, 2018).