## **Biomedical Application of Non-Thermal Atmospheric Pressure Plasma and Its Usefulness** Guest Editor: Tetsuo Adachi

## Introduction to serial reviews: Biomedical application of non-thermal atmospheric pressure plasma and its usefulness

## Tetsuo Adachi\*

Laboratory of Clinical Pharmaceutics, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan

(Received 2 September, 2016; Accepted 14 September, 2016; Published online 17 December, 2016)

Plasma is an ionized gas and is described as the fourth state of matter. Electrons, positive and negative ions, radicals, neutral and charged molecules, and photons have been identified in plasma. Plasma may be observed in daily life, e.g., as sun, lighting in thunderstorms, and the Northern lights, and has been applied to technology and industries, e.g., in low-energy light bulbs, surface treatment technologies, air purifiers, and flat panel displays.<sup>(1)</sup>

The treatment of aqueous samples with plasma results in the generation of a large amount of reactive oxygen species (ROS) including hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), superoxide anion (O<sub>2</sub><sup>-</sup>), hydroxyl radical ('OH), singlet oxygen (<sup>1</sup>O<sub>2</sub>), and other species that are generated from oxygen in atmospheric air or solution.<sup>(2-4)</sup> Reactive nitrogen species (RNS) such as nitric oxide (NO) have also been detected.<sup>(5,6)</sup>

"Plasma medicine" is a leading and innovative field combining life science and clinical medicine, and its potential has been demonstrated in various applications such as wound healing,<sup>(7)</sup>

## References

- von Woedtke T, Reuter S, Masur K, Weltmann K-D. Plasma on medicine. *Physics Reports* 2013; 530: 291–320.
- 2 Starikovskiy A. Physics and chemistry of plasma-assisted combustion. *Phil Trans R Soc* 2015; 373: 20150074.
- 3 Gorbanev Y, O'Connell D, Chechik V. Non-thermal plasma in contact with water: the origin of species. *Chem Eur J* 2016; 22: 3496–3505.
- 4 Panngom K, Baik KY, Nam MK, Han JH, Rhim H, Choi EH. Preferential killing of human lung cancer cell lines with mitochondrial dysfunction by nonthermal dielectric barrier discharge plasma. *Cell Death Dis* 2013; 4: e642.
- 5 Naïtali M, Kamgang-Youbi G, Herry JM, Bellon-Fontaine MN, Brisset JL. Combined effects of long-living chemical species during microbial inactivation using atmospheric plasma-treated water. *Appl Environ Microbiol* 2010; **76**: 7662–7664.
- 6 Kalghatgi S, Kelly CM, Cerchar E, et al. Effects of non-thermal plasma on mammalian cells. PLoS One 2011; 6: e16270.
- 7 Haertel B, von Woedtke T, Weltmann KD, Lindequist U. Non-thermal atmospheric-pressure plasma possible application in wound healing. *Biomol Ther (Seoul)* 2014; 22: 477–490.
- 8 Kalghatgi S, Friedman G, Fridman A, Clyne AM. Endothelial cell proliferation is enhanced by low dose non-thermal plasma through fibroblast growth factor-2 release. *Ann Biomed Eng* 2010; **38**: 748–757.
- 9 Joshi SG, Cooper M, Yost A, et al. Nonthermal dielectric-barrier discharge

blood coagulation,<sup>(8)</sup> sterilization,<sup>(9)</sup> dental cavity treatments,<sup>(10)</sup> and cancer treatments.<sup>(11,12)</sup> In these studies, a low dose of plasma was shown to induce the proliferation of cells, while a high dose induced apoptosis as well as necrosis in cells.<sup>(8)</sup>

ROS and RNS are regarded as the key substances in plasma that affect cell responses.<sup>(13–16)</sup> Recent studies demonstrated that plasma exerts effects on cancer cells not only directly, but also by the indirect treatment of cells with previously prepared medium irradiated by plasma, termed plasma-activated medium (PAM).<sup>(11,12,17–20)</sup> These findings suggest that the relatively short-lived ROS/RNS produced in media by plasma irradiation may be converted to other relatively long-lived species such as  $H_2O_2$ , nitrate/nitrite (NO<sub>x</sub>), which endow PAM with high and sustainable reactivity.<sup>(4,21)</sup>

In this serial review, basic research on plasma, its reactivity with cell membranes, and its application to the inactivation of bioparticles, blood coagulation, and cancer therapy will be discussed.

plasma-induced inactivation involves oxidative DNA damage and membrane lipid peroxidation in *Escherichia coli. Antimicrob Agents Chemother* 2011; **55**: 1053–1062.

- 10 Rupf S, Idlibi AN, Marrawi FA, et al. Removing biofilms from microstructured titanium ex vivo: a novel approach using atmospheric plasma technology. PLoS One 2011; 6: e25893.
- 11 Utsumi F, Kajiyama H, Nakamura K, et al. Effect of indirect nonequilibrium atmospheric pressure plasma on anti-proliferative activity against chronic chemo-resistant ovarian cancer cells in vitro and in vivo. PLoS One 2013; 8: e81576.
- 12 Tanaka H, Mizuno M, Ishikawa K, et al. Plasma-activated medium selectively kills glioblastoma brain tumor cells by down-regulating a survival signaling molecule, AKT kinase. *Plasma Med* 2011; 1: 265–277.
- 13 Vandamme M, Robert E, Lerondel S, *et al.* ROS implication in a new antitumor strategy based on non-thermal plasma. *Int J Cancer* 2012; **130**: 2185– 2194.
- 14 Ahn HJ, Kim KI, Hoan NN, et al. Targeting cancer cells with reactive oxygen and nitrogen species generated by atmospheric-pressure air plasma. PLoS One 2014; 9: e86173.

\*To whom correspondence should be addressed. E-mail: adachi@gifu-pu.ac.jp

- 15 Lee Y, Kim K, Kang KT, Lee JS, Yang SS, Chung WH. Atmosphericpressure plasma jet induces DNA double-strand breaks that require a Rad51mediated homologous recombination for repair in *Saccharomyces cerevisiae*. *Arch Biochem Biophys* 2014; **560**: 1–9.
- 16 Okazaki Y, Wang Y, Tanaka H, et al. Direct exposure of non-equilibrium atmospheric pressure plasma confers simultaneous oxidative and ultraviolet modifications in biomolecules. J Clin Biochem Nutr 2014; 55: 207–215.
- 17 Hoentsch M, Bussiahn R, Rebl H, et al. Persistent effectivity of gas plasmatreated, long time-stored liquid on epithelial cell adhesion capacity and membrane morphology. PLoS One 2014; 9: e104559.
- 18 Adachi T, Tanaka H, Nonomura S, Hara H, Kondo S, Hori M. Plasma-

activated medium induced A549 cell injury by a spiral apoptotic cascade involving the mitochondrial-nuclear network. *Free Radic Biol Med* 2015; **79**: 28–44.

- 19 Adachi T, Nonomura S, Horiba M, et al. Iron stimulates plasma-activated medium-induced A549 cell injury. Sci Rep 2016; 6: 20928.
- 20 Hara H, Taniguchi M, Kobayashi M, Kamiya T, Adachi T. Plasma-activated medium-induced intracellular zinc liberation causes death of SH-SY5Y cells. *Arch Biochem Biophys* 2015; 584: 51–60.
- 21 Kurake N, Tanaka H, Ishikawa K, et al. Cell survival of glioblastoma grown in medium containing hydrogen peroxide and/or nitrite, or in plasma-activated medium. Arch Biochem Biophys 2016; 605: 102–108.