

プラズマ医療研究の最前線 Frontiers of Plasma Medicine Research

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Low temperature plasmas have been applied to a wide range of industrial processes such as fabrication of micro and nano-scale structures on the surfaces of semiconductor chips and thin film deposition for surface coating of various materials. Recently, as one of such applications, use of low-temperature plasmas for medical treatment and material processing for medical applications has attracted much attention in the plasma research community. In this presentation, the recent trend and progresses in this field, known collectively as “plasma medicine,” will be reviewed.

In general, research in plasma medicine may be categorized into three subfields. One of them is surface modification/treatment of biomedical materials [1-3]. For example, surfaces of petri dishes (made of polystyrene) are typically pretreated by oxygen plasmas. Surface coating of metal artificial joints by hydroxyapatite is often done with plasma spraying with the use of thermal plasmas. Surface polymerization by plasma CVD (chemical vapor deposition) is also widely studied for the formation of biocompatible films.

Another subfield that is also widely studied is plasma sterilization [4-6]. Including commercial products such as plasma-based air purifiers, this subfield has seen much technological development in recent years in areas beyond medical equipment although the fundamental mechanisms of bactericidal effects by plasmas have yet to be understood better. Furthermore, there are other sources for infectious diseases that are still difficult to remove by plasmas, such as spore forming bacteria, viruses, and prions, and inactivation of them is still a topic of active research in this subfield. Usually difficulty of treating such infection sources by plasmas lies in the fact that, in reality, removal of them needs to be done without damaging the environments (such as human bodies or medical equipment) where they exist, and often in a cost effective manner.

The third but not least subfield of the three is

study on therapeutic or clinical use of plasmas. This subfield is often considered as plasma medicine in narrow sense. Probably the best known plasma device that is already in use for surgical operations is argon plasma coagulator (APC) [7-9]. For this device, heat generated by Ar plasma is used for cauterization or thermal ablation of tissues. In this sense, the APC is similar to an electrical scalpel. The essential difference between them is that the tip of an APC device is contactless with tissues.

In current research of the above subfield, however, low-temperature, non-cauterizing plasma devices have been much of the focus for scientific and technological development. Recent studies have shown that application of low-temperature plasmas directly to living cells and tissues has some therapeutic effects such as blood coagulation, angiogenesis, prevention of organ adhesion, and wound healing [10]. The origin of such effects is considered to be reactive species (RS) generated by plasmas. Under typical discharge conditions in air, plasma efficiently generates reactive oxygen species (ROS) /reactive nitrogen species (RNS) such as atomic oxygen O, hydroxyl radical OH, hydroperoxyl (or perhydroxyl) radical HOO, singlet oxygen $^1\text{O}_2$, and nitric oxide (or nitrogen monoxide) NO. Such chemically reactive species are often generated from endogenous sources in living bodies and play crucial roles in controlling cell signaling pathways and maintaining homeostasis. In this sense, perhaps it is not surprising that externally generated ROS/RNS by plasmas can have some significant effects on living cells and tissues under certain conditions.

In this presentation, first addressing non-experts of plasma medicine, the author will review general goals and motivations of research as well as various plasma generating systems used in this field. Second, addressing those who already work or have strong interest in this field, the author will briefly review some of the latest discoveries and hot topics in plasma medicine. Then, as an example of a

specific research topic, some latest results that the author and his collaborators have obtained in their study on plasma application for orthopedics will be discussed at length [11].

It has been known that chemically reactive species generated by atmospheric-pressure plasmas (APPs) can enhance cell proliferation. As an example of orthopedic application of plasma effects, effects of APP application on growth of mesenchymal stem cells and other cells that are of interest in orthopedics will be discussed first. In the experiments, three conditions were tested. In the first condition, low-temperature APPs were directly injected into a culture medium [Dulbecco's Modified Eagle Medium (DMEM) with fetal bovine serum (FBS)] containing cells and the cells were cultured in the same medium for a few days. In the second condition, immediately after the medium containing cells was exposed to plasmas, the plasma-exposed medium was discarded and replaced with a fresh medium of the same kind and the cells were cultured for a few days in the new medium. In the third condition, plasma jets were injected into the same medium without cells, and then the cells were cultured in the plasma treated medium for a few days. In each case, cell proliferation (or cell death in the case of overexposure of the plasmas) was observed, which indicates that the presence of either chemically reactive species dissolved in the medium or solutes modified by such chemically reactive species affects cell viability. The level of free radical generation in the medium was examined by dROMs tests [12] and correlation between cell proliferation and oxidative stress were observed.

As a second example, plasma treatment of artificial bones made of interconnected porous calcium hydroxyapatite (IP-CHA) will be discussed. It has been found that dielectric barrier discharge (DBD) plasma treatment at a relatively low pressure with an admixture of He and O₂ gases significantly improves hydrophilicity of the surfaces of IP-CHA, particularly that of wall surfaces of the internal pores. IP-CHA has been clinically used as a material for bone substitutes in bone tissue regeneration. Various in-vitro and in-vivo experiments have shown that plasma-treated IP-CHA exhibits higher osteoconductivity. Especially Alkaline Phosphatase (ALP) Assays of Adipose Derived Stem Cells (ADSC) cultured inside plasma-treated IP-CHA have indicated plasma treatment enhances differentiation of such cells. Figure 1 shows photographs of IP-CHA implant into calvarial defects of rats [13].

The experimental studies by the author and his

colleagues discussed above were performed in collaboration with Prof. H. Yoshikawa and his group members at the School of Medicine, Osaka University.

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Figure 1 : Critical calvarial defects in rats were filled with a untreated IP-CHA disc in left and a plasma-treated IP-CHA disc in right. It is seen that increased hydrophilicity by plasma treatment allows rapid penetration of blood into IP-CHA [13].