Numerical modeling of selective cell death induction by plasma-induced reactive species

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Abstract: We have developed a numerical model of an intracellular biochemical system to simulate the selectivity of plasma-induced cell death for normal and cancer cells. Numerical results showed that a certain dose of plasma-derived reactive species selectively kill only cancer cells while leaving normal cells alive.

1. Introduction

In the field of plasma medicine, application for cancer therapy is one of the important themes. It has become clear that low-temperature plasmas can selectively induce cell death of cancer cells only, with minimal effect on normal cells [1,2]. However, the factors which plasma causes the selectivity of cell death, and optimal plasma irradiation requirements for effectively inducing cell death in cancer cells only, remain poorly understood. Therefore, an approach from theoretical and mathematical perspectives, i.e., quantitative elucidation with numerical modeling, is required. In this study, we extended our previous numerical model [3] to examine the effects of low-temperature plasma on the selectivity of cell death for normal and cancer cells.

2. Modeling

Time-dependent zero-dimensional kinetic calculation is performed, in which a set of ODE is solved. 300 chemical and biochemical agents, with 600 reactions are taken into account. The difference in the intracellular conditions for normal and cancer cells are implemented in the metabolic function, ferrous (Fe^{2+}) levels, glutathione (GSH) levels and DNA repairment capability (Table 1). Various biochemical reactions are induced when plasma-generated species penetrate into the cells. Here, the oxidative reactions and its counterpart antioxidant reactions have to be modeled properly. When the concentration of intracellular reactive species is excessive, the DNA would be damaged. Fatal DNA damage activates the p53 gene, which represses Bcl-2 protein while enhances Bax protein. The Bax protein causes mitochondrial dysfunction. Then, apoptotic cascade is initiated, leading to cell death.

3. Results

Apoptosis is induced when p53 is sufficiently activated by DNA damage. Figure 1 shows the response of p53 gene in normal and cancer cells against the degree of plasma-dose (H_2O_2). For less plasma-dose (H_2O_2 < 50μM) condition, the p53 activation is suppressed. In contrast, the p53 is fully activated in both normal and cancer cells when plasma-dose is excessive (H_2O_2 > 90μM). At the intermediate plasma-dose (50μM < H_2O_2 < 90μM) condition, the p53 of cancer cells is activated. These results indicate that the suitable plasma-dose can induce the selective cell death induction. The H_2O_2 concentration indexed here are in agreement with the results of various experimental studies [4,5].

Table. 1. The differences of intracellular conditions between normal and cancer cells.

Characteristics	Normal	Cancer
Intake	Low	High
ROS generation	Low	High
Ferrous	Low	High
Glutathione	Low	High
DNA repair	Fast	Slow

4. Conclusion

We developed a numerical model of an intracellular biochemical system to simulate the selectivity of plasma-induced cell death for normal and cancer cells. Numerical results showed that a certain dose of plasma-derived reactive species selectively kill only cancer cells while leaving normal cells alive.

Acknowledgement

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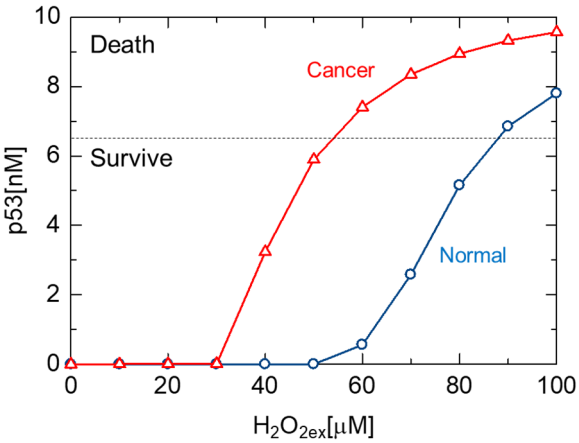

Fig. 1. The activation of the p53 gene against the degree of plasma-dose (H_2O_2).
(Blue : Normal cells, Red : Cancer cells)