

## News Release

### Title

Non-thermal atmospheric pressure plasma activates lactate in Ringer's solution for anti-tumor effects

### Key Points

○Plasma-activated Ringer's lactate solution has anti-tumor effects on glioblastoma and ovarian cancer cells.

○Lactate of four components is the only anti-tumor component in Ringer's lactate solution that is activated by plasma.

○Plasma-activated Ringer's acetate solution also has anti-tumor effects.

### Summary

Professor Masaaki Mizuno (Center for Advanced Medicine and Clinical Research) in Nagoya University Hospital (Director: Naoki Ishiguro, M.D., Ph.D.), Professor. Fumitaka Kikkawa (Department of Obstetrics and Gynecology) in Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.), and Professor Masaru Hori (Director of Plasma Medical Science Global Innovation Center, Institute of Innovation for Future Society) in Nagoya University, and their collaborators investigated the ability of plasma-activated Ringer's lactate solution for cancer therapy.

Non-thermal atmospheric pressure plasma is a novel approach for wound healing, blood coagulation, and cancer therapy. A recent discovery in the field of plasma medicine is that non-thermal atmospheric pressure plasma not only directly but also indirectly affects cells via plasma-treated liquids. This discovery has led to the use of non-thermal atmospheric pressure plasma as a novel chemotherapy. We refer to these plasma-treated liquids as plasma-activated liquids. We chose Ringer's solutions to produce plasma-activated liquids for clinical applications. *In vitro* and *in vivo* experiments demonstrated that plasma-activated Ringer's lactate solution has anti-tumor effects, but of the four components in Ringer's lactate solution, only lactate exhibited anti-tumor effects through activation by non-thermal plasma. Nuclear magnetic resonance analyses indicate that plasma irradiation generates acetyl and pyruvic acid-like groups in Ringer's lactate solution. Overall, these results suggest that plasma-activated Ringer's lactate solution is promising for chemotherapy.

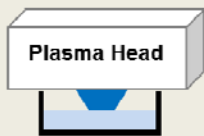


### Research Background

Non-thermal atmospheric pressure plasma is a novel approach for wound healing, blood coagulation, and cancer therapy. A recent discovery in the field of plasma medicine is that non-thermal atmospheric pressure plasma not only directly but also indirectly affects cells via plasma-treated liquids. This discovery has led to the use of non-thermal atmospheric pressure plasma as a novel chemotherapy. We refer to these plasma-treated liquids as plasma-activated liquids. We chose Ringer's solutions to produce plasma-activated liquids for clinical applications.

## Research Results

In this study, we created plasma-activated Ringer's lactate solution and investigated its anti-tumor effects on cancer cells. Ringer's lactate solution has only four components in addition to water: lactate, NaCl, KCl, and CaCl<sub>2</sub>.

**(a)**

	Plasma-treated 2X solutions	Complementary 2X solutions	Treat cells with mixed 1X solutions for 1h
			
①	N/A	NaCl, KCl, CaCl <sub>2</sub> , L-sodium lactate	Untreated Lactec
②	NaCl	KCl, CaCl <sub>2</sub> , L-sodium lactate	NaCl-GOF
③	KCl	NaCl, CaCl <sub>2</sub> , L-sodium lactate	KCl-GOF
④	CaCl <sub>2</sub>	NaCl, KCl, L-sodium lactate	CaCl <sub>2</sub> -GOF
⑤	L-sodium lactate	NaCl, KCl, CaCl <sub>2</sub>	L-sodium lactate-GOF
⑥	KCl, CaCl <sub>2</sub> , L-sodium lactate	NaCl	NaCl-LOF
⑦	NaCl, CaCl <sub>2</sub> , L-sodium lactate	KCl	KCl-LOF
⑧	NaCl, KCl, L-sodium lactate	CaCl <sub>2</sub>	CaCl <sub>2</sub> -LOF
⑨	NaCl, KCl, CaCl <sub>2</sub>	L-sodium lactate	L-sodium lactate-LOF
⑩	NaCl, KCl, CaCl <sub>2</sub> , L-sodium lactate	Milli-Q	Plasma-treated Lactec
⑪	Milli-Q	NaCl, KCl, CaCl <sub>2</sub> , L-sodium lactate	Treated water

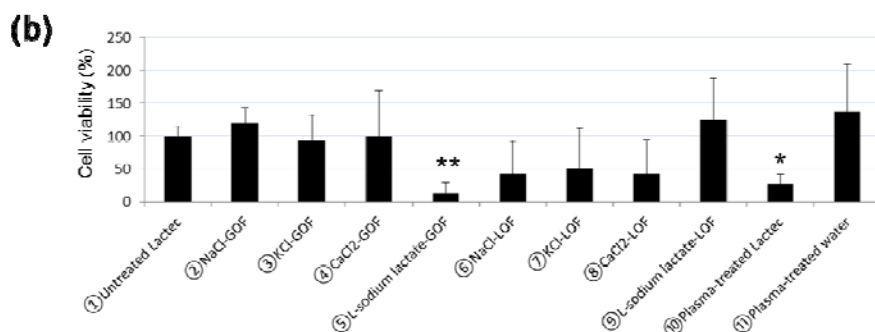


Figure 1: Identification of components in PAL having anti-tumor effects.

Systematic analyses demonstrated that lactate is the only anti-tumor component in Ringer's lactate solution that is activated by plasma (Figure 1), and that plasma irradiation generates acetyl and pyruvic acid-like groups in the solution.

## Research Summary and Future Perspective

As Ringer's solutions are already used clinically, we developed a new PAM for clinical applications by irradiating Ringer's lactate solution with plasma. In the present study, we demonstrated that plasma-activated Ringer's lactate solution has anti-tumor effects *in vitro* and *in vivo*. Moreover, Ringer's lactate solution is a simple solution containing only four components in addition to water. We found that only the L-sodium lactate irradiated by plasma had anti-tumor effects. For clinical applications, the components of solutions

should be as simple as possible, and the species that are responsible for anti-tumor effects should be known. These results represent significant progress toward the use of plasma-activated liquids for clinical applications.

### **Publication**

H. Tanaka, K. Nakamura, M. Mizuno, K. Ishikawa, K. Takeda, H. Kajiyama, F. Utsumi, F. Kikkawa, M. Hori, Non-thermal atmospheric pressure plasma activates lactate in Ringer's solution for anti-tumor effects, *Scientific Reports*, November 8, 2016.

### **Japanese ver.**

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