Cancer Research and Oncology: Open Access
Received: Jul 11, 2016, Accepted: Aug 09, 2016, Published: Aug 13, 2016
Cancer Res Oncol, Volume 2, Issue 4
http://crescopublications.org/pdf/crooa/CROOA-2-021.pdf
Article Number: CROOA-2-021

Letter to Editor **Open Access**

Response to the Letter to the Editor re: Ogawa, Y. Paradigm Shift in Radiation Biology/Radiation Oncology – Exploitation of the "H_2O_2 Effect" for Radiotherapy Using Low-LET (Linear Energy Transfer) Radiation such as X-rays and High-Energy Electrons. Cancers, 2016, 8, 28

Yasuhiro Ogawa*

Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Hyogo 675-8555, Japan

***Corresponding Author:** Yasuhiro Ogawa, Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Hyogo 675-8555, Japan; Tel: +81-79-497-7001; Fax: +81-79-438-3757; E-mail: ogaway@kochi-u.ac.jp

Citation: Yasuhiro Ogawa (2016) Response to the Letter to the Editor re: Ogawa, Y. Paradigm Shift in Radiation Biology/Radiation Oncology – Exploitation of the "H_2O_2 Effect" for Radiotherapy Using Low-LET (Linear Energy Transfer) Radiation such as X-rays and High-Energy Electrons. Cancers, 2016, 8, 28.Cancer Res Oncol 2: 021.

Keywords: Hydrogen peroxide; Radio sensitizer; Sodium hyaluronate; Radiotherapy; KORTUC; Radiation therapy; H_2O_2 effect; Direct effect; Indirect effect.

I read the Letter [1] to the Editor written by Prof. CJ Koch re: Ogawa, Y. Cancers 2016, 8, E28 [2] with great interest. Since I am a clinical radiation oncologist with limited knowledge of radiation chemistry, I wonder if there may have been some misleading statements in my review [2].

The purpose of my review was to address the strong interaction at the cellular level between hydrogen peroxide and X-rays that was first observed in our research in the human osteosarcoma HS-Os-1 and prostate cancer PC-3 cell lines under conditions of extreme resistance to either drugs or 30-Gy single-dose X-rays alone [3-6]. Sensitization to ionizing radiation by 0.1 mM hydrogen peroxide was achieved that did not involve the DNA damage response that normally mediates cell killing. The mechanism was shown to involve lysosomal rupture with release of powerful oxidants, including Fe^{+++} ions that damage mitochondrial membranes and activate early apoptosis [7]. As shown in Figure 4 in our previous paper [7], ferric ion-induced lysosomal rupture was visualized 4 hours after X-ray irradiation with hydrogen peroxide in PC-3 prostate cancer cell cultures. Stabilization of lysosomal metalloproteins is achieved by raising intralysosomal pH from 4.5 to >6 with addition of NH_4Cl to culture medium. This finding abrogates the sensitization of X-ray irradiation by hydrogen peroxide under ambient conditions [7,8].

In the Letter to the Editor, Prof. Koch states that the mechanisms of apoptotic death for irradiated lymphocytes are not entirely clear, since apoptosis can arise from either DNA damage or membrane damage, and the latter has been implicated over certain dose ranges even for more resistant tumor cells. Concerning the mechanisms of apoptotic death for irradiated lymphocytes, we have extensively studied the mechanisms and have elucidated them in our previous papers [9-16]. In fact, human peripheral lymphocytes are considered to be representative in terms of their high level of radio sensitivity, as shown in Figure 2 in our paper [1]. As indicated by the Letter to the Editor by Prof. Koch, there were some errors in Figures 2-4 of our paper [1], especially with respect to illustrations of the nuclei. All of the illustrations of nuclei in Figures 2-4 should be replaced with that in Figure 1.

As shown in our previous paper, radiation kills human peripheral T cells by a Fas-independent mechanism [16], and radiation-induced reactive oxygen species were formed prior to oxidative DNA damage in these cells [13,14]. Besides the involvement of lysosomal membrane destabilization in X-ray irradiation-induced apoptosis of human peripheral T cells [9-11], we have also shown mitochondrial cytochrome C release following dysfunction of mitochondrial membrane potentials after irradiation of these cells [15]. Therefore, potential mitochondrial membrane dysfunction following X-ray irradiation is considered to occur simultaneously with lysosomal membrane dysfunction in the apoptotic mechanism of human peripheral lymphocytes.

In the Letter to the Editor, Prof. Koch states that the amount of hydrogen peroxide produced by 10 Gy is only about 3μM under aerobic conditions, similar to the hydroxyl radical yield [17]. However, this statement is absolutely not in agreement with his explanation on lines 45-47 of page 2 in the letter, as shown below. In ultrapure water and at high dose rates, it is certainly possible for two hydroxyl radicals to produce hydrogen peroxide [17], but this should not mean it should be considered a reaction appropriate to the cell, where essentially all hydroxyl radicals will react with organic molecules, and where hydrogen peroxide arises from electron capture by oxygen, with subsequent dismutation of the superoxide radical by superoxide dismutase. Actually, the amount of hydrogen peroxide produced by X-rays apparently seems to be underestimated because of the powerful activities of peroxidases and catalase, which most malignant neoplasms usually have in their cells [18,19]. As described by Prof. Koch, catalase directly converts hydrogen peroxide to water and oxygen. Therefore, even if vast hydroxyl radicals were yielded by X-ray irradiation, most of the produced hydrogen peroxide might be decreased in a short time following irradiation by the powerful activities of the peroxidases and catalase.

Moreover, the description by Prof. Koch on line 1 of page 2 stating that, as indicated above, radiation-induced tumor cell toxicity is primarily mediated through DNA damage [20] is actually very curious, as it lacks modern evidence, and needs to be more precisely framed. Additionally, the description by Prof. Koch on lines 12-14 of page 2 stating that, since hydroxyl radicals react at diffusion-controlled rates, their production in the cytoplasm or elsewhere is of no consequence (this was established many decades ago using site-specific isotope decay, which is not acceptable in my view) [21]. As I indicated above, sensitization to X-ray irradiation by 0.1 mM hydrogen peroxide was achieved and did not involve the DNA damage response that normally mediates cell killing [5,7]. The mechanism was shown to involve lysosomal rupture with release of powerful oxidants, including Fe^{+++} ions that damage mitochondrial membranes and activate early apoptosis.

Furthermore, the description by Prof. Koch on lines 34-37 stating that, in that discussion, "the extremely poor performance of hydrogen peroxide as a sensitizer was noted, thus we are unaware of any data that suggest hydrogen peroxide, or inhibiting the action of peroxidases, has anything to do with the oxygen effect or the indirect effect, and no references on the same subject were given for the alternate suggestion by Ogawa [1]", is absolutely not acceptable in my view, as described above.

In conclusion, basic concepts that were established by early work in radiation biology have been inhibiting the appropriate development of modern radiation biology in terms of contributing to clinical radiation oncology. Therefore, modern technologies should be introduced into modern radiation biology for basic research, especially for elucidating other action mechanisms of low LET radiation sources, such as X-rays and electrons, besides direct and indirect effects.

Concerning the anti-oxidant systems that most malignant neoplasms possess, all researchers in the field of radiation biology/radiation oncology should recognize the powerful activities of peroxidases and/or catalase present in almost all tumor tissues. All researchers in the field of immunohistochemistry [18,19,22-27] using fresh cancer tissues know the power of peroxidases. As defense systems of cancers, the most important factor is considered to be anti-oxidative enzymes, such as the many kinds of peroxidases and catalase. It is assumed that the law of Bergonie and Tribondeau can be explained by the degree of power of the peroxidases and/or catalase in the target tumor tissue.

To elucidate the action mechanisms of our newly developed radio sensitization method (KORTUC), which has already demonstrated remarkable therapeutic effects for patients with various types of neoplasms [28-41], it is vitally important to promote good free-radical and hydrogen peroxide-based chemistry, as also stated by Prof. Koch [1], to promote improvements of the therapeutic effects of cancer therapy/radiation therapy.

Acknowledgements

This work was partially supported by a grant-in-aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (25461916).

References

1. Koch CJ. Letter to the Editor Re: Ogawa Y. Cancers, 2016, 8, 28. Cancers 8: E53, 2016.
2. Ogawa Y. Paradigm shift in radiation biology/radiation oncology – Exploitation of the "H_2O_2 effect" for radiotherapy using low-LET (linear energy transfer) radiation such as X-rays and high-energy electrons. Cancers 8, E28, 2016.
3. Ogawa Y, Takahashi T, Kobayashi T, Kariya S, Nishioka A, Hamasato S, Moriki T, Seguchi H, Yoshida S, Sonobe H. Immunocytochemical characteristics of human osteosarcoma cell line HS-Os-1: Possible implication in apoptotic resistance against irradiation. Int. J. Mol. Med. 14(3): 397-403, 2004.
4. Ogawa Y, Takahashi T, Kobayashi T, Kariya S, Nishioka A, Ohnishi T, Saibara T, Hamasato S, Tani T, Seguchi H, Yoshida S, Sonobe H. Apoptotic-resistance of the human osteosarcoma cell line HS-Os-1 to irradiation is converted to apoptotic-susceptibility by hydrogen peroxide: a potent role of hydrogen peroxide as a new radio sensitizer. Int. J. Mol. Med. 12(6): 845-850, 2003.
5. Ogawa Y, Takahashi T, Kobayashi T, Kariya S, Nishioka A, Mizobuchi H, Noguchi M, Hamasato S, Tani T, Seguchi H, Yoshida S, Sonobe H. Mechanism of apoptotic resistance of human osteosarcoma cell line, HS-Os-1, against irradiation. Int. J. Mol. Med.12(4): 453-458, 2003.
6. Ogawa Y, Takahashi T, Kobayashi T, Kariya S, Nishioka A, Mizobuchi H, Noguchi M, Hamasato S, Tani T, Seguchi H, Yoshida S, Sonobe H. Mechanism of hydrogen peroxide-induced apoptosis of the human osteosarcoma cell line HS-Os-1. Int. J. Mol. Med. 12(4): 459-463, 2003.
7. Kariya S, Sawada K, Kobayashi T, Karashima T, Shuin T, Nishioka A, Ogawa Y. Combination treatment of hydrogen peroxide and X-rays induces apoptosis in human prostate cancer PC-3 cells. Int. J. Radiat. Oncol. Biol. Phys. 75(2): 449-454, 2009.
8. Ogawa Y, Kobayashi T, Kariya S, Nishioka A, Nakayama K, Seguchi H, Yoshida S. Prevention of hydrogen peroxide-induced apoptosis of human peripheral T cells by a lysosomotropic iron chelator, ammonium chroride. Int. J. Mol. Med. 14(6): 1007-1013, 2004.
9. Ogawa Y, Kobayashi T, Nishioka A, Kariya S, Ohnishi T, Hamasato S, Seguchi H, Yoshida S. Reactive oxygen species-producing site in radiation and hydrogen peroxide-induced apoptosis of human peripheral T cells: Involvement of lysosomal membrane destabilization. Int. J. Mol. Med. 13(5): 655-660, 2004.
10. Ogawa Y, Kobayashi T, Nishioka A, Kariya S, Ohnishi T, Hamasato S, Seguchi H, Yoshida S. Reactive oxygen species-producing site in hydrogen peroxide-induced apoptosis of human peripheral T cells: Involvement of lysosomal membrane destabilization. Int. J. Mol. Med. 13(3): 383-386, 2004.
11. Ogawa Y, Kobayashi T, Nishioka A, Kariya S, Ohnishi T, Hamasato S, Seguchi H, Yoshida S. Reactive oxygen species-producing site in radiation-induced apoptosis of human peripheral T cells: involvement of lysosomal membrane destabilization. Int. J. Mol. Med. 13(1): 69-73, 2004.
12. Ogawa Y, Takahashi T, Kobayashi T, Toda M, Nishioka A, Kariya S, Seguchi H, Yamamoto H, Yoshida S. Comparison of radiation-induced reactive oxygen species formation in adult articular chondrocytes and that in human peripheral T cells: Possible implication in radio sensitivity. Int. J. Mol. Med. 11(4): 455-459, 2003.
13. Ogawa Y, Kobayashi T, Nishioka A, Kariya S, Hamasato S, Seguchi H, Yoshida S. Radiation-induced reactive oxygen species formation prior to oxidative DNA damage in human peripheral T cells. Int. J. Mol. Med. 11(2): 149-152, 2003.
14. Ogawa Y, Kobayashi T, Nishioka A, Kariya S, Hamasato S, Seguchi H, Yoshida S. Radiation-induced oxidative DNA damage, 8-oxoguanine, in human peripheral T cells. Int. J. Mol. Med. 11(1): 27-32, 2003.
15. Ogawa Y, Nishioka A, Kobayashi T, Kariya S, Hamasato S, Saibara T, Nakayama K, Seguchi H, Yoshida S. Mitochondrial cytochrome c release in radiation-induced apoptosis of human peripheral T cells. Int. J. Mol. Med. 10(3): 263-268, 2002.
16. Ogawa Y, Nishioka A, Inomata T, Yoshida S, Nakayama K, Kataoka S. Radiation kills human peripheral T cells by a Fas-independent mechanism. Int. J. Mol. Med. 2(4): 403-408, 1998.
17. Von Sonntag C. The Chemical Basis of Radiation Biology; Taylor and Francis: London, UK, 1987.

18. Ogawa Y, Maeda T, Seguchi H, Hamada N, Inomata T, Yoshida S, Kishimoto S, Saito H. Infiltration of Leu-3a+3b-positive lymphocytes and expression of human leukocyte antigen DR on tumor tissue induced by radiation therapy. Oncology (Basel), 45(1): 18-20, 1988.
19. Ogawa Y, Inomata T, Nishioka A, Maeda T, Seguchi H, Kishimoto S, Saito H, Hirota J, Osaki T. Changes in the Ki-67 labeling rates of head and neck squamous cell carcinomas during preoperative radiation therapy. Oncology (Basel), 49(6): 450-453, 1992.
20. Cheng Y, Li F, Mladenov E, Iliakis G. The yield of DNA double strand breaks determined after exclusion of those forming from heat-labile lesions predicts tumor cell radio sensitivity to killing. Radioth. Oncol. 116: 366-373, 2015.
21. Waters RL, Hofer KG. Radionuclide toxicity in cultured mammalian cells: Elucidation of the primary site for radiation-induced division delay. Radiat. Res. 69: 348-358, 1977.
22. Nishioka A, Ogawa Y, Inomata T, Maeda T, Seguchi H. Fibronectin expression in cancer tissues from patients undergoing radiation therapy. Histol. Histopathol. 8(3): 457-462, 1993.
23. Hamada N, Ogawa Y, Seguchi H, Terashima M, Nishioka A, Inomata T, Yoshida S, Kishimoto S, Saito H. Immunohistochemical study of p53 expression in cancer tissues from patients undergoing radiation therapy. Histol. Histopathol. 10(3): 611-617, 1995.
24. Ogawa Y, Nishioka A, Hamada N, Terashima M, Inomata T, Yoshida S, Seguchi H, Kishimoto S. Changes of mutant-type p53 expression in squamous cell carcinoma of the head and neck during radiation therapy and its clinical significance: comparison of an immunohistochemical method and PCR-SSCP assay. Oncol. Rep. 5(5): 1053-1059, 1998.
25. Ogawa Y, Nishioka A, Hamada N, Terashima M, Inomata T, Yoshida S, Seguchi H, Kishimoto S. Immunohistochemical study of c-fos-positive lymphocytes infiltrated into human squamous cell carcinomas of the head and neck radiation therapy and its clinical significance. Clin. Cancer Res. 3: 2301-2307, 1997.
26. Ogawa Y, Nishioka A, Hamada N, Terashima M, Inomata T, Yoshida S, Seguchi H, Kishimoto S. Expression of Fas (CD95/APO-1) antigen induced by radiation therapy for diffuse B-cell lymphoma: immunohistochemical study. Clin. Cancer Res. 3: 2211-2216, 1997.
27. Ogawa Y, Nishioka A, Hamada N, Terashima M, Inomata T, Yoshida S, Seguchi H, Kishimoto S. Immunhistochenmical study of c-fos-positive lymphocytes infiltrated into human squamous cell carcinomas of the head and neck during radiation therapy and its clinical significance. Clin. Cancer Res. 3: 2301-2307, 1997.
28. Tokuhiro S, Ogawa Y, Tsuzuki K, Akima R, Ue H, Kariya S, Nishioka A. Development of a new enzyme-targeting radio sensitizer (KORTUC) containing hydrogen peroxide for intratumoral injection for patients with low linear energy transfer (LET) radio resistant neoplasms. Oncol. Lett. 1: 1025-1028, 2010.
29. Ogawa Y, Kubota K, Ue H, Kataoka Y, Tadokoro M, Miyatake K, Tsuzuki K, Yamanishi T, Itoh S, Hitomi J, Hamada N, Kariya S, Fukumoto M, Nishioka A, Inomata T. Phase I study of a new radio sensitizer containing hydrogen peroxide and sodium hyaluronate for topical tumor injection: A new enzyme-targeting radio sensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II). Int. J. Oncol. 34: 609-618, 2009.
30. Ogawa Y, Kubota K, Ue H, Tadokoro M, Matsui R, Yamanishi T, Hamada N, Kariya S, Nishioka A, Nakajima H, Tarutani M, Sano S. Safety and effectiveness of a new enzyme-targeting radio sensitization treatment (KORTUC II) for intratumoral injection for low-LET radio resistant tumors. Int. J. Oncol. 39: 553-560, 2011.
31. Tsuzuki A, Ogawa Y, Kubota K, Tokuhiro S, Akima R, Yaogawa S, Itoh K, Yamada Y, Sasaki T, Onogawa M, Yamanishi T, Kariya S, Nogami M, Nishioka A, Miyamura M. Evaluation of changes in tumor shadows and micro calcifications on mammography following KORTUC II, a new radio sensitization treatment without any surgical procedure for elderly patients with stage I and II breast cancer. Cancers 3: 3496-3505, 2011.
32. Hitomi J, Kubota K, Ogawa Y, Hamada N, Murata Y, Nishioka A. Non-surgical therapy and radiologic assessment of stage I breast cancer treatment with novel enzyme-targeting radiosensitization: Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas. Exp. Ther. Med. 1(5): 769-775, 2010.

33. Ogawa Y, Kubota K, Aoyama N, Yamanishi T, Kariya S, Hamada N, Nogami M, Nishioka A, Onogawa M, Miyamura M. Non-surgical breast-conserving treatment (KORTUC-BCT) using a new radio sensitization method (KORTUC II) for patients with stage I or II breast cancer. Cancers 7: 2277-2289, 2015.
34. Miyatake K, Kubota K, Ogawa Y, Hamada N, Murata Y, Nishioka A. Non-surgical care for locally advanced breast cancer: radiologically assessed therapeutic outcome of a new enzyme-targeting radio sensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II) with systemic chemotherapy. Oncol. Rep. 24(5): 1161-1168, 2010.
35. Nishioka A, Ogawa Y, Mityatake K, Tadokoro M, Nogami M, Hamada N, Kubota K, Kariya S, Kohsaki T, Saibara T, Okabayashi T, Hanazaki K. Safety and efficacy of image-guided enzyme-targeting radio sensitization and intraoperative radiotherapy for locally advanced unresectable pancreatic cancer. Oncol. Lett. 8(1): 404-408, 2014.
36. Aoyama N, Ogawa Y, Yasuoka M, Takahashi M, Iwasa H, Miyatake K, Yamanishi T, Hamada N, Tamura T, Nishioka A, Yamagami T. Therapeutic response to a novel enzyme-targeting radio sensitization treatment (Kochi Oxydol-Radaition Therapy for Unresectable Carcinomas) in patients with recurrent breast cancer. Oncol. Lett. 12(1): 29-34, 2016.
37. Hayashi N, Ogawa Y, Kubota K, Okino K, Akima R, Morita-Tokuhiro S, Tsuzuki A, Yaogawa S, Nishioka A, Miyamura M. Computed tomography demonstration of the production and distribution of oxygen gas following intratumoral injection of a new radio sensitizer (KORTUC) for patients with breast cancer – is intratumoral injection not an ideal approach to solve the major problem of tumor hypoxia in radiotherapy? Cancers (Basel) 8(4): E43, 2016.
38. Yaogawa S, Ogawa Y, Morita-Tokuhiro S, Tsuzuki A, Akima R, Itoh K, Morio K, Yasunami H, Onogawa M, Kariya S, Nogami M, Nishioka A, Miyamura M. Serial assessment of therapeutic response to a new radio sensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II), in patients with stage I/II breast cancer using breast contrast-enhanced magnetic resonance imaging. Cancers (Basel) 8(1): E1, 2016.
39. Morita-Tokuhiro S, Ogawa Y, Yokota N, Tsuzuki A, Oda H, Ishida N, Aoyama N, Nishioka A. Development of a novel enzyme-targeting radio sensitizer (New KORTUC) using a gelatin-based hydrogel instead of a sodium hyaluronate. Cancers (Basel) 8(1): E10, 2016.
40. Aoyama N, Ogawa Y, Iwasa H, Tadokoro M, Yamanishi T, Tamura T, Kobayashi K, Kariya S, Miyamura M, Yamagami T. Possible adverse effects of non-surgical breast-conserving treatment (KORTUC-BCT) using a new radio sensitization method (KORTUC II) for patients with stage I or II breast cancer. Cancer Res. Oncol. 2(2): E014, 2016.
41. Aoyama N, Ogawa Y, Kubota K, Ohgi K, Kataoka Y, Tadokoro M, Yamanishi T, Ohnishi T, Hamada N, Kariya S, Tamura T, Nogami M, Nishioka A, Onogawa M, Miyamura M. Therapeutic response to a new enzyme-targeting radio sensitization treatment (KORTUC-SC) for patients with chemotherapy-resistant supraclavicular lymph node metastasis. J. Cancer Res. Ther. 1(9): 215-219, 2013.