Dose-Response:
An International Journal
July-September 2018:1-7

DOI: 10.1177/1559325818784719
journals.sagepub.com/home/dos
SAGE

Recovery From Rheumatoid Arthritis Following 15 Months of Therapy With Low Doses of Ionizing Radiation: A Case Report

Shuji Kojima[1], Mitsutoshi Thukimoto[1], Jerry M. Cuttler[2], Kiyomi Inoguchi[3], Takahiro Ootaki[4], Noriko Shimura[5], Hironobu Koga[6], and Akihisa Murata[6]

Abstract

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that occurs commonly in old people. Hot spring radon therapy is widely practiced in Central Europe and Japan for relief from the painful symptoms. The usual duration of a spa treatment is a week or two, and the relief is temporary. This article reports on the near-complete recovery of a patient who had been suffering from RA for 10 years. The patient received 15 months of low-dose radon and γ-radiation therapy in a room that reproduced the conditions of a radon spa. The daily 40-minute exposure in the therapy room was supplemented by ten 6-minute radio-nebulizer treatments. The inflammation markers C-reactive protein and matrix metalloproteinase 3 declined strongly to the normal level of 0.07 mg/dL and the near-normal level of 48.9 ng/mL, respectively. After the patient's return to good health, the frequency of the visits was reduced to twice each month. The patient's protection systems appear to have adapted to stimulated conditions, sufficiently to sustain the recovery from RA. Such a long-term course of treatments and follow-up maintenance could be carried out in any hospital that has these low-dose radiation therapy rooms. The therapy could be scheduled to suit patient availability.

Keywords

rheumatoid arthritis, low-dose radiation, radon therapy room, hormesis, immune cells, Treg cells

Introduction

Radon therapy has been widely employed in Central Europe, Russia, and Japan.[1-8] Patients with age-related illnesses have been receiving traditional radon hot spring treatments for more than a century.[9] In Europe, "bathing" in tunnels, mines, steam, inhalation, and so on, has been practiced. This therapy has included drinking radon water and inhaling radon gas. Falkenbach and colleagues have reviewed studies to analyze the effect of radon therapy on pain in rheumatic diseases.[10] In a meta-analysis, the pooled data showed no difference immediately after treatment ($P < .13$). However, significant pain reduction was observed in the radon group compared to the control group at 3 months ($P < .02$) and 6 months ($P < .002$) after treatment.[10] The mechanism was not discussed.

An Italian research group conducted radon-enriched hot spring water therapy for asthma, upper nasal congestion, and allergic rhinitis.[11] Patients were treated for 12 to 28 days by inhalation of radon gas from high-concentration radon water. They were evaluated at baseline and after treatment. After 2 weeks of treatment, nasal resistance decreased, flow increased, mucociliary clearance enhanced, ciliated to muciparous cell ratio increased, and % forced expiratory volume (in 1 second) increased in patients with asthma. Inhalation therapy, rich in radon, improves objective

[1] Department of Radiation Biosciences, Faculty of Pharmaceutical Sciences, Tokyo University of Science (TUS), Noda-shi, Chiba, Japan
[2] Cuttler and Associates Inc, Vaughan, Ontario, Canada
[3] Drainage Co, Ltd, Minoo-shi, Osaka, Japan
[4] Ootaki Clinic, Toshima-ku, Osaka, Japan
[5] Faculty of Pharmaceutical Sciences, Ohu University, Koriyama, Japan
[6] Lead and Company Co, Ltd, Minami-ku, Yokohama, Japan

Received 06 April 2018; received revised 27 May 2018; accepted 29 May 2018

Corresponding Author:
Shuji Kojima, Department of Radiation Biosciences, Faculty of Pharmaceutical Sciences, Tokyo University of Science (TUS), 2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan.
Email: skjma@jcom.zaq.ne.jp

indicators of nasal function in allergic rhinitis and chronic rhinosinusitis and causes alleviation of pulmonary obstruction in asthma.[11]

In Japan, radon treatment using radon volatilizing from radon-rich water is carried out at Misasa Medical Center (Okayama University Hospital) for patients with reactive oxygen species (ROS)-related diseases such as arteriosclerosis, osteoarthritis, and bronchial asthma. They are based on previous reports that low-dose radiation induces antioxidant capacity.[12-14]

Using a therapy room in Tokyo that was designed to reproduce the conditions of the Bad Gastein radon hot spa, we provided radon therapy successfully to 2 patients with advanced breast cancer and to a patient who suffered from severe inflammation.[15,16] In this article, we describe the case of a patient who had been suffering from rheumatoid arthritis (RA) for 10 years. Following 15 months of daily therapy using another therapy room in Osaka, she made a near-complete recovery. We also review and discuss the mechanism in relation to the results obtained from animal studies.

Treatment Facility and Equipment

Therapy Room

The therapy room is designed to reproduce the conditions of a health spa, that is, a warm, moist atmosphere of low-dose ionizing radiation, like those in the Bad Gastein radon hot spa. Because the duration of a visit to a health spa is usually limited from days to weeks, the benefit received is relatively small and short-lived. A therapy room located in a clinic in Osaka allows a patient, living nearby, to receive daily treatments, under carefully controlled conditions, for as long a time as needed to achieve a significant, long-lasting improvement. Furthermore, periodic 1-day treatments can be provided to maintain the improvement against aging-induced regression to the patient's previous condition.

The room, supplied by Lead & Company Co (Yokohama, Japan), has walls that contain natural monazite. This radioactive mineral, excavated from a mountainous area of Japan, contains phosphate of thorium and rare earth elements. The average γ-radiation dose rate in the room was 11 μGy per hour, and the average concentration of radon radioactivity was 200 000 Bq/m^3, as measured using Alpha-Scint-1 monitor (TRACERLAB, Koeln, Germany).

Radio-Nebulizer

Uranium ore (150 g) is placed into an 8-L stainless steel container. Then 4 L of water is added and left to stand for about 12 hours, as radon gas emanating from the ore dissolved in the water. Radon water of 15 mL is poured into the cup of an ultrasonic nebulizer. The patient inhales all of the vapor from the cup (about 6 minutes).

Case Report: Patient With RA Recovers After 15 Months of Radiation Therapy

The patient was 63 years of age when she was diagnosed with RA at a major hospital. During her treatments with bucillamine, loxoprofen, and methotrexate from September 2006 until January 2016—almost 10 years, she did not experience improvement as her condition deteriorated nor did she obtain significant relief from the increasingly painful symptoms. Water accumulated on her right knee; walking became excruciatingly painful and tiring; her whole body sagged. Removing the shoes from her swollen feet was a very difficult task. Eventually, she could not raise her arms above her shoulders, had painful swelling in both wrists, and could hardly do housework such as cooking.

In 2016, at age 73, she heard that low doses of (ionizing) radiation might help. She visited the Ootaki Clinic in Osaka and accepted the clinician's recommendation to try low-dose radiation treatments in a therapy room (hormesis room) followed by radio-nebulizer treatments. It was a major commitment on her part to continue receiving these treatments for an indefinitely long time, starting on February 8, 2016. For 40 minutes each day, 5 days every week, the patient occupied the small therapy room, where the temperature and relative humidity were maintained at about 40°C and 70%, respectively. Using The International Commission on Radiological Protection formula,[17] effective dose $= 6.7 \times 10^{-6}$ mSv per Bq·h·m^{-3}, the effective dose of each 40-minute exposure was calculated to be about 0.4 mSv. About 30 minutes after leaving the therapy room, the patient received 10 consecutive treatments with a radio-nebulizer. She received the nebulizer treatments 6 days every week. She felt no symptomatic side effects from any of these treatments.

By July 2016, the inflammation had subsided and the pain throughout her body almost disappeared. The daily treatments ended on May 13, 2017. To prevent regression to her previous condition, she began to receive a treatment in the therapy room followed by 10 nebulizer treatments twice every month. By February 2018, at age 75, the patient's appetite had returned to normal; her muscular strength was restored, also to her legs and right knee. A happy smile appeared on her face.

The markers in Figure 1 clearly indicated a significant improvement. When the treatments started on February 8, 2016, the clinician did not measure the markers for RA because he did not anticipate the dramatic improvements that he began to observe later on. The inflammatory marker C-reactive protein (CRP), measured on July 7, 2016, was 4.03 mg/dL. It declined to 0.69 mg/dL on January 28, 2017, and to the normal value of 0.07 mg/dL on May 13, 2017. As for the RA blood marker matrix metalloproteinase 3 (MMP-3), its value was 1,680 ng/mL on July 7, 2016. It decreased to 61.8 ng/mL in January 28, 2017, and to the almost normal level of 48.9 ng/mL on May 13, 2017.

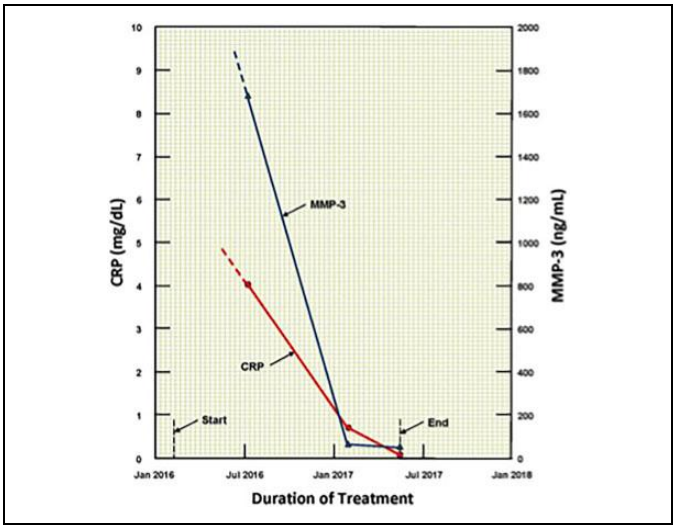

Figure 1. Changes in inflammatory rheumatoid markers, CRP and MMP-3, during the low-dose radiation treatments. The patient remained in the therapy room for 40 minutes a day, 5 days a week. She also inhaled radon-containing vapor from the radio-nebulizer, 10 times consecutively (6 minutes each time), 6 days a week. CRP indicates C-reactive protein; MMP, matrix metalloproteinase 3.

Discussion

Rheumatoid arthritis is one of the typical collagen diseases. It is an inflammatory autoimmune disease in which self-immunity mainly affects the joints of arms and legs, thereby causing joint pain and joint deformation. The effectiveness of radon hot spring treatment against the pain suffered by patients with RA was shown in the statistical analysis by Falkenbach et al.[10] In the Misasa Medical Center, patients stay in the high-concentration radon room without bathing. The room temperature is 42°C, and the radon concentration is about 2080 Bq/m^3 (100 times the average natural background radiation level). Every 2 days, steam from the hot spring is inhaled for 40 minutes under high humidity (90%) conditions. The effective dose is 50 to 67 μSv. The inhibitory effects of radon inhalation on ROS-related pathology have been reported[12-14]; human trials have demonstrated that radon treatment has anti-inflammatory and pain-reducing effects. These benefits were further confirmed in animal models of carrageenan-induced inflammatory paw edema and formalin-induced irritation pain.[17,18] However, it is regrettable that the descriptions of mechanisms that are related to pathological condition improvement are insufficient in these reports. In this case report, we write about our discovery of the very significant improvement in the health of a patient with severe RA following her long-term therapy in a room with conditions similar to the Bad Gastein radon hot spa. It can be expected from the changes in the pathological conditions and the rheumatism-related markers. MMP-3 inflammation occurs in the synovial cells covering the inside of various joints of the whole body of patients with RA, progressively spreading from the synovium to the cartilage and bone, eventually destroying the joint itself and causing joint deformation. Since MMP-3 is produced from proliferated synovial cells in RA, it is thought that this protein directly plays a major role in cartilage destruction. Therefore, if the serum MMP-3 concentration in a patient with RA shows a high value or rises, it is predicted that the progress of joint destruction will be fast. On the contrary, the value decreases when the disease state stabilizes due to the therapeutic effect. Although serum MMP-3 concentration does not increase in joint diseases such as osteoarthritis, gout, and many collagen diseases, it may be high even in systemic lupus erythematosus (SLE), glomerulonephritis, and the like, and the specificity in diagnosis of RA is not necessarily high. Therefore, it is usually combined with a CRP test, which can judge degree of inflammation, in clinical diagnosis of RA.[19] In doing so, clinicians obtain more accurate information of bone destruction, inflammation, and pathology of the patient. From the recovery of the inflammatory markers CRP and MMP-3 as described above, we can easily predict that other inflammatory cytokines tumor necrosis factor-α (TNF-α), interferon-γ (INF-γ), and interleukin-6 (IL-6) previously obtained from our animal experiments will change in a similar manner. Also, the decline of the markers after treatment correlated well with the relief experienced by the patient from the painful symptoms of RA and the happy expression on her face.

Regarding the mechanism of the rheumatic condition improvement effect by low-dose radiation, the following 8 mechanisms have been reviewed in the article written by Calabrese et al in 2013[20]: nitric oxide (NO)/inducible nitric oxide synthase (iNOS) declines,[21,22] decline of ROS,[23] increase of heme-oxygenase,[24] induction of apoptosis,[25] increase of TNF-α and transforming growth factor-β1 (TGF-β-)1,[26] activity of transcription factor (NF-κ-B) and activated protein 1,[27] decreased adhesion of leukocytes and polymorphonuclear leukocyte (PNM) to endothelial cells,[28,29] and increase of regulatory T (Treg) cells.[30,31] Among these mechanisms, our research group has proposed the involvement of Treg cells in the low-dose, radiation-induced rheumatic condition improvement effect. Based on these basic experimental data, we attempted to improve the effect on human rheumatic disease. Thus, we would like to describe the details of the process leading up to this mechanism in this report. For details of other mechanisms, refer to cited documents. The detail mechanisms at the cellular and molecular level of the effect of improving rheumatic disease by radon treatment, shown in a human, were inferred from the results obtained by animal experiments. We anticipated some benefit from the observed effects of low-dose γ-irradiation on our rheumatism model mice. In animal models, we had investigated the effects on several autoimmune diseases by a 0.5 Gy γ-irradiation—a small dose that is significantly lower than a high dose, but slightly higher than the low-dose definition. For the SLE model (MRL-*lpr/lp*) mouse, the RA model, and the like, γ-irradiation inhibited the production of inflammatory cytokines and autoantibodies and showed a remarkable pathological condition-improving effect. Involvement of Treg cells in its mechanism is suggested.[30,32,33] That is, Treg cells were implicated in the improvement of autoimmune disease by the

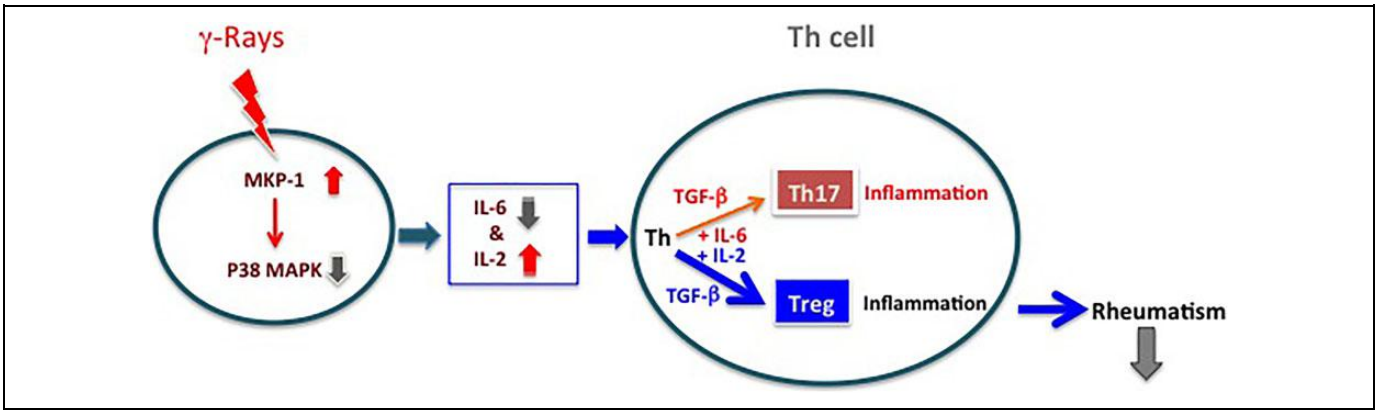

Figure 2. Surmised mechanism of attenuated autoimmune diseases by low-dose ionizing radiation. Whole-body ionizing irradiation against autoimmune diseases → increase in MKP-1 expression in macrophages → suppression of production of inflammatory cytokines (TNF-α, IL-6, etc) → Th17 decrease and Treg cells increase → inflammatory cytokines and autoantibody production reduction → attenuation of autoimmune pathology and inflammatory rheumatoid markers. MKP-1 indicates mitogen-activated protein kinase phosphatase 1.

irradiation. Regulatory T cells constitute a distinct subset that prevents immune pathology via suppression of pathogenic T cells, such as Th17 cells. Regulatory T cells have a critical function in the regulation of autoimmune diseases, including RA and collagen-induced arthritis (CIA), while Th17 cells, one of the pathogenic T cells, have an aggravating function.[34-38] Regulatory T cells express CD4, IL-2 receptor α-chain, and transcriptional factor Foxp3.[39] Th17 cells and Treg cells are both differentiated from naive $CD4^+$ T cells, and differentiation to Treg versus Th17 cells is found to be mutually exclusive. Naive $CD4^+$ T cells will be differentiated to Th17 cells in the presence of TGF-β with IL-6 and to Treg cells in the presence of TGF-β and IL-2.[40-43] Based on these reports, we subsequently investigated attenuation of CIA by low-dose γ-ray irradiation, and involvement of Treg cells in its mechanisms were examined in CIA model mouse.[44] Collagen-induced arthritis is the most widely used as a human RA model and shows pathology similar to human RA, such as synovitis, pannus formation, bone destruction, and the like.

It is found that the inflammatory cytokines TNF-α, INF-γ, and IL-6 serve as important triggers as the onset of this condition involves the activation of T cells and the production of autoantibodies.[45-47] Arthritis was induced by sensitizing male DBA/1J mice with bovine type II collagen as an emulsion with complete Freund's adjuvant via the tail vein and sensitizing them. This model mouse was given whole-body γ-irradiation at a dose of 0.5 Gy, once a week, from the third day before collagen sensitization and then irradiated for 8 weeks. As a result, arthritis developed more than 4 weeks after collagen sensitization in the CIA disease group, and the disease state score reached the maximum value at around 8 weeks. The irradiation was observed to delay the onset of the pathological condition by around 2 weeks, along with the inhibition of foot swelling and bone destruction. The incidence of CIA was also ameliorated. Splenomegaly and increased production of TNF-α, INF-γ, IL-6, and anti-II collagen antibodies, induced by arthritis, were also markedly reduced by γ-irradiation. In addition, analysis of the population of T cells revealed that the irradiation caused a significant increase of Treg cells in comparison with the CIA disease model group. Gamma-irradiation-induced Treg cell upregulation would be caused by the reduction of IL-6 production, since IL-6 is involved in the differentiation of naive $CD4^+$ T cells into Treg cells. In the basic experiments using the CIA mouse model, we would consider that low-dose γ-ray irradiation can ameliorate the pathological conditions in RA through induction of Treg cells.

Subsequently, we examined the inhibitory mechanism of inflammatory cytokine production via mitogen-activated protein kinase (MAPK) phosphatase 1 (MKP-1) expression. Activation of extracellular signal-regulated kinase1/2 (ERK1/2) of MAPK has been reported as an effect on cells by ionizing radiation.[48,49] Meanwhile, we revealed that MKP-1, which dephosphorylates and inactivates MAPK, is activated by γ-irradiation, leading to inactivating ERK1/2 and p38 MAPK. Since p38 MAPK is involved in the production of inflammatory cytokines (TNF-α and IL-6), the influence of the irradiation on TNF-α production via p38 MAPK activation was examined using macrophages in order to clarify the molecular mechanism of anti-inflammatory action by γ-irradiation.[50] As a result, phosphorylation (activation) of ERK1/2 and p38 MAPK was reduced by γ-irradiation 15 minutes after the irradiation, suggesting the increased activity of MKP-1 by γ-irradiation. As expected, increased expression of MKP-1 was also observed 15 minutes after the irradiation. Based on these results, 0.5 Gy γ-irradiation showed the inhibitory effect of p38 MAPK activation via increased MKP-1 expression. It is known that activation of p38 MAPK is involved in TNF-α production, one of inflammatory cytokines. Then, the effect of irradiation on p38 MAPK activation after lipopolysaccharide (LPS) stimulation was investigated. It was shown that p38 MAPK activation by LPS was suppressed in irradiated cells. Next, the effect of suppressing TNF-α production by γ-irradiation was examined. TNF-α production was suppressed in the irradiated cells as expected. From these results, it was suggested that MKP-1

increase by irradiation causes dephosphorylation of p38 MAPK, suggesting the possibility of suppression of TNF-α production. The involvement of MKP-1 in TNF-α production using MKP-1 knocking down cells by small interfering RNA was further examined. TNF-α production increased in MKP-1 knockdown cells, suggesting that p38 MAPK activation by LPS and TNF-α production downstream of LPS may be suppressed via increased MKP-1 expression by γ-irradiation.

A mechanism of improvement of autoimmune disease of radiation including γ-rays was surmised from our previous basic experiments in animal models. A reduction of IL-6 production may correct the balance that was inclined to Th17 cells to the Treg cell differentiation direction, and the scheme shown in Figure 2 can be evaluated.

We also elucidate the effect of improving autoimmune diseases through this increase in Treg cell proportion in other autoimmune disease model mice such as experimental autoimmune encephalomyelitis model.[51] Since the increase in the Treg cells ratio occurs commonly in the autoimmune disease improvement effect by small dose γ-rays, it is highly likely that it plays an important role in the disease condition improvement effect. We believe that this increase in Treg cells ratio is a new paradigm in an autoimmune pathology improvement effect, using low doses of ionizing radiation. We suggest that Treg cells are also involved as a mechanism of improvement of autoimmune pathology in patients, by low-dose radiation room therapy. In addition, the increase in Treg cells is considered to be closely related to the mechanism of improvement of rheumatic pathology by low-dose radiation as described by Calabrese and Calabrese.[20] Therefore, it is important to investigate this therapy as a treatment for refractory autoimmune diseases.

Conclusions

Rheumatoid arthritis is a painful and debilitating disease that affects many old people. Some travel a great distance to visit a radon hot spring spa and receive a short-lived benefit. However, most patients are treated with various pharmaceutical remedies that relieve symptoms but do not change the illness.

This case report describes the achievement of a significant reversal of this disease. The daily exposure in the special therapy room and the supplementary radio-nebulizer treatments produced a major change after 15 months. Moreover, it appears possible to sustain the improvement by a periodic maintenance treatment, twice monthly.

This very important discovery should be confirmed by repeating the long-term therapy on other patients and measuring the inflammatory rheumatoid markers at frequent intervals, for example, monthly, starting from the beginning of the treatment. Health science centers around the world should begin to investigate this alternative form of treatment and perform proper clinical studies because it may lead to lasting cures for many important diseases.

The development of the special, low-dose radiation therapy room is very important. It allows long-term treatments to be carried out in hospitals or clinics located anywhere in the world. It makes this form of treatment accessible to all patients at an affordable cost.

Acknowledgments

The authors would like to thank their patient (H.H.) for granting us permission to report her case.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Franke A, Reiner L, Resch KL. Long-term benefit of radon spa therapy in the rehabilitation of rheumatoid arthritis: a randomised, double-blinded trial. *Rheumatol Int*. 2007;27(8):703-713.
2. Verhagen AP, Bierma-Zeinstra SM, Boers M, et al. Balneotherapy (or spa therapy) for rheumatoid arthritis. An abridged version of Cochrane Systematic Review. *Eur J Phys Rehabil Med*. 2015; 51(6):833-847.
3. Franke A, Reiner L, Pratzel HG, Franke T, Resch KL. Long-term efficacy of radon spa therapy in rheumatoid arthritis—a randomized, sham-controlled study and follow-up. *Rheumatology (Oxford)*. 2000;39(8):894-902.
4. Franke A, Franke T. Long-term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre ImuRa trial. *Rheumatol Int*. 2013;33(11):2839-2850.
5. Forestier R, Françon A. Crenobalneotherapy for limb osteoarthritis: systematic literature review and methodological analysis. *Joint Bone Spine*. 2008;75(2):138-148.
6. Forestier R, Erol Forestier FB, Françon A. Current role for spa therapy in rheumatology. *Joint Bone Spine*. 2017;84(1):9-13.
7. van Tubergen A, Landewé R, van der Heijde D, et al. Combined spa-exercise therapy is effective in patients with ankylosing spondylitis: a randomized controlled trial. *Arthritis Rheum*. 2001; 45(5):430-438.
8. Becker K.Health effects of high radon environments in Central Europe: another test for the LNT hypothesis. *Nonlinearity Bio Tox Med*. 2003;1(1):3-35.
9. Becker K. One century of radon therapy. *Int J Low Radiation*. 2004;1(3):334-357.
10. Falkenbach A, Kovacs J, Franke A, Jörgens K, Ammer K. Radon therapy for the treatment of rheumatic diseases—review and meta-analysis of controlled clinical trials. *Rheumatol Int*. 2005; 25(3):205-210.
11. Passali D, Gabelli G, Passali CP, Mösges R, Bellussi LM. Radon-enriched hot spring water therapy for upper and lower respiratory tract inflammation. *Otolaryngol Pol*. 2017;71(4):6-12.
12. Yamaoka K, Mitsunobu F, Hanamoto K, Mori S, Tanizaki Y, Sugita K. Study on biologic effects of radon and thermal therapy on osteoarthritis. *J Pain*. 2004;5(1):20-25.

13. Mitsunobu F, Yamaoka K, Hanamoto K, et al. Elevation of antioxidant enzymes in the clinical effects of radon and thermal therapy for bronchial asthma. *J Radiat Res*. 2003;44(2):95-99.
14. Kataoka T. Study of antioxidative effects and anti-inflammatory effects in mice due to low-dose X-irradiation or radon inhalation. *J Radiat Res*. 2013;54(4):587-596.
15. Kojima S, Tsukimoto M, Shimura N, Koga H, Murata A, Takara T. Treatment of cancer and inflammation with low-dose ionizing radiation: three case reports. *Dose-Response*. 2017;15(1):1-7. doi: 10.1177/1559325817697531.
16. Kojima S, Cuttler JM, Shimura N, Koga H, Murata A, Kawashima A. Present and future prospects of radiation therapy using α-emitting nuclides. *Dose Response*. 2018;16(1):1-8. doi:10.1177/1559325817747387.
17. Kataoka T, Teraoka J, Sakoda A, et al. Protective effects of radon inhalation on carrageenan-induced inflammatory paw edema in mice. *Inflammation*. 2012;35(2):713-722.
18. Yamato K, Kataoka T, Nishiyama Y, Taguchi T, Yamaoka K. Antinociceptive effects of radon inhalation on formalin-induced inflammatory pain in mice. *Inflammation*. 2013;36(2):355-363.
19. Ally M, Hodkinson B, Meyer B, Musenge E, Tikly M, Anderson R. Serum matrix metalloproteinase-3 in comparison with acute phase proteins as a marker of disease activity and radiographic damage in early rheumatoid arthritis. *Mediat Inflammat*. 2013; 2013(Article ID 183653):6 pages.
20. CalabreseEJ, Calabrese V. Reduction of arthritic symptoms by low dose radiation therapy (LD-RT) is associated with an anti-inflammatory phenotype. *Int J Radiat Biol*. 2005;89(4):278-286.
21. Calabrese EJ. Nitric oxide: biphasic dose responses. *Crit Rev Toxicol*. 2001;31(4-5):489-502.
22. Hildebrandt G, Loppnow G, Jahns J, et al. Inhibition of the iNOS pathway in inflammatory macrophages by low-dose X-irradiation in vitro. *Strahlenther Onkol*. 2003;179(3):158-166.
23. Schaue D, Marples B, Trott KR. The effects of low-dose X-irradiation on the oxidative burst in stimulated macrophages. *Int J Radiat Biol*. 2002;78(7):567-576.
24. Hildebrandt G, Radlingmayr A, Rosenthal S, et al. Low-dose radiotherapy (LD-RT) and the modulation of iNOS expression in adjuvant induced arthritis in rats. *Int J Radiat Biol*. 2003; 79(12):993-1001.
25. Kern P, Keilholz L, Forster C, Seegenschmiedt MH, Sauer R. In vitro apoptosis in peripheral blood mononuclear cells induced by low-dose radiotherapy displays a discontinuous dose-dependence. *Int J Radiat Biol*.1999;75(8):995-1003.
26. Schaue D, Jahns J, Hildebrandt G, Trott KR. Radiation treatment of acute inflammation in mice. *Int J Radiat Biol*. 2005;81(9): 657-667.
27. Rödel F, Keilholz L, Herrmann M, et al. Activator protein 1 shows a biphasic induction and transcriptional activity after low dose X-irradiation in EA.hy.926 endothelial cells. *Autoimmunity*. 2009;42(4):343-345.
28. Kern PM, Keilholz L, Forster C, Hallmann R, Herrmann M, Seegenschmiedt MH. Low-dose radiotherapy selectively reduces adhesion of peripheral blood mononuclear cells to endothelium in vitro. *Radiother Oncol*. 2000;54(3):273-282.
29. Rödel F, Schaller U, Schultze-Mosgau S, et al. The induction of TGF-β 1 and NF-κ B parallels a biphasic time course of leukocyte/endothelial cell adhesion following low-dose X-irradiation. *Strahlenther Onkol*. 2004;180(4):194-200.
30. Nakatsukasa H, Tsukimoto M, Tokunaga A, Kojima S. Repeated irradiation attenuates collagen-induced arthritis via up-regulation of regulatory T cells but not by damaging lymphocytes directly. *Radiat Res*. 2010;174(3):313-324.
31. Weng L, Williams RU, Vieira PL, Screaton G, Feldmann M, Dazzi F. The therapeutic activity of low-dose irradiation on experimental arthritis depends on the induction of endogenous regulatory T cell activity. *Ann Rheum Dis*. 2010;69(8): 1519-1526.
32. Tanaka T, Tago F, Fang SP, Shimura N, Kojima S. Repeated 0.5 Gy gamma-ray irradiation attenuates autoimmune manifestation in MRL-*lpr/lpr* mice. *Int J Radiat Biol*. 2005;81(10):731-740.
33. Tago F, Tsukimoto M, Nakatsukasa H, Kojima S. Repeated 0. 5-Gy gamma irradiation attenuates autoimmune disease in MRL-*lpr/lpr* mice with suppression of $CD3^+CD4^-CD8^-B220^+$ T-Cell proliferation and with up-regulation of $CD4^+CD25^+$ $Foxp3^+$ regulatory T cells. *Radiat Res*. 2008;169(1):59-66.
34. Sakaguchi S. Naturally arising $CD4^+$ regulatory T cells for immunologic self-tolerance and negative control of immune response. *Ann Rev Immunol*. 2004;22:531-562.
35. Baecher-Allen C, Hafler DA. Human regulatory T cells and their role in autoimmune disease. *Immunol Rev*. 2006; 212(1):203-216.
36. Morgan ME, Sutmuller RP, van Duivenvoorde LM, et al. $CD25^+$ cell depletion hastens the onset of severe disease in collagen-induced arthritis. *Arthritis Rheum*. 2003;48(5):1452-1460.
37. Londei M. Role of regulatory T cells in experimental arthritis and implication for clinical use. *Arthritis Res Ther*. 2005;7(3): 118-120.
38. Sato K, Suematsu A, Okamoto K, et al. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. *J Exp Med*. 2006;203(12):2673-2682.
39. Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of $CD4^+CD25^+$ regulatory T cells. *Nat Immunol*. 2003;4(3):330-336.
40. Chen W, Jin W, Hardegen N, et al. Conversion of peripheral $CD4^+CD25^-$ naïve T cells to $CD4^+CD25^+$ regulatory by TGF-beta induction of transcription factor Foxp3. *J Exp Med*. 2003; 198(12):1875-1886.
41. Nelson BH. IL-2, regulatory T cells, and tolerance. *J Immunol*. 2004;172(7):3983-3988.
42. Bettelli E, Carrier Y, Gao W, et al. Reciprocal development pathways of the generation of pathogenic effector Th17 and regulatory T cells. *Nature*. 2006;441(7090):235-238.
43. Veldhoen M, Hocking RJ, Atkins C, Locksley RM, Stockinger B. TGFβ in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. *Immunity*. 2006;24(2):179-1891.
44. Nakatsukasa H, Tsukimoto M, Ohshima Y, Tago F, Masada A, Kojima S. Suppressing effect of low-dose gamma-ray irradiation on collagen-induced arthritis. *J Radiat Res*. 2008;49(4):381-389.
45. Firestein GS. Evolving concepts of rheumatoid arthritis. *Nature*. 2003;85(6937):356-361.

46. Feldmann M, Brennan FM, Maini RN. Rheumatoid arthritis. *Cell*. 1996;85(3):307-310.
47. Gravallese EM. Bone destruction in arthritis. *Ann Rheum Dis*. 2002;61(2):ii84-ii86.
48. Schmidt-Ullrich RK, Mikkelsen RB, Dent P, et al. Radiation-induced proliferation of the human A431 squamous carcinoma cells is dependent on EGFR tyrosine phosphorylation. *Oncogene*. 1997;15(10):1191-1197.
49. Nyati MK, Feng FY, Maheshwari D, et al. Ataxia telangiectasia mutated down-regulates phospho-extracellular signal-regulated kinase 1/2 via activation of MKP-1 in response to radiation. *Cancer Res*. 2006;66(22):11554-11559.
50. Tsukimoto M, Homma T, Mutou Y, Kojima S. 0.5 Gy γ-ray irradiation suppresses production of TNF-α through up-regulation of MKP-1 in mouse macrophage RAW264.7 cells. *Radiat Res*. 2009;171(2):219-224.
51. Tsukimoto M, Nakatsukasa K, Sugawara K, Yamashita Y, Kojima S. Repeated 0.5-Gy γ irradiation attenuates experimental autoimmune encephalomyelitis with up-regulation of regulatory T cells and suppression of IL-17 production. *Radiat Res*. 2008;170(4):429-436.