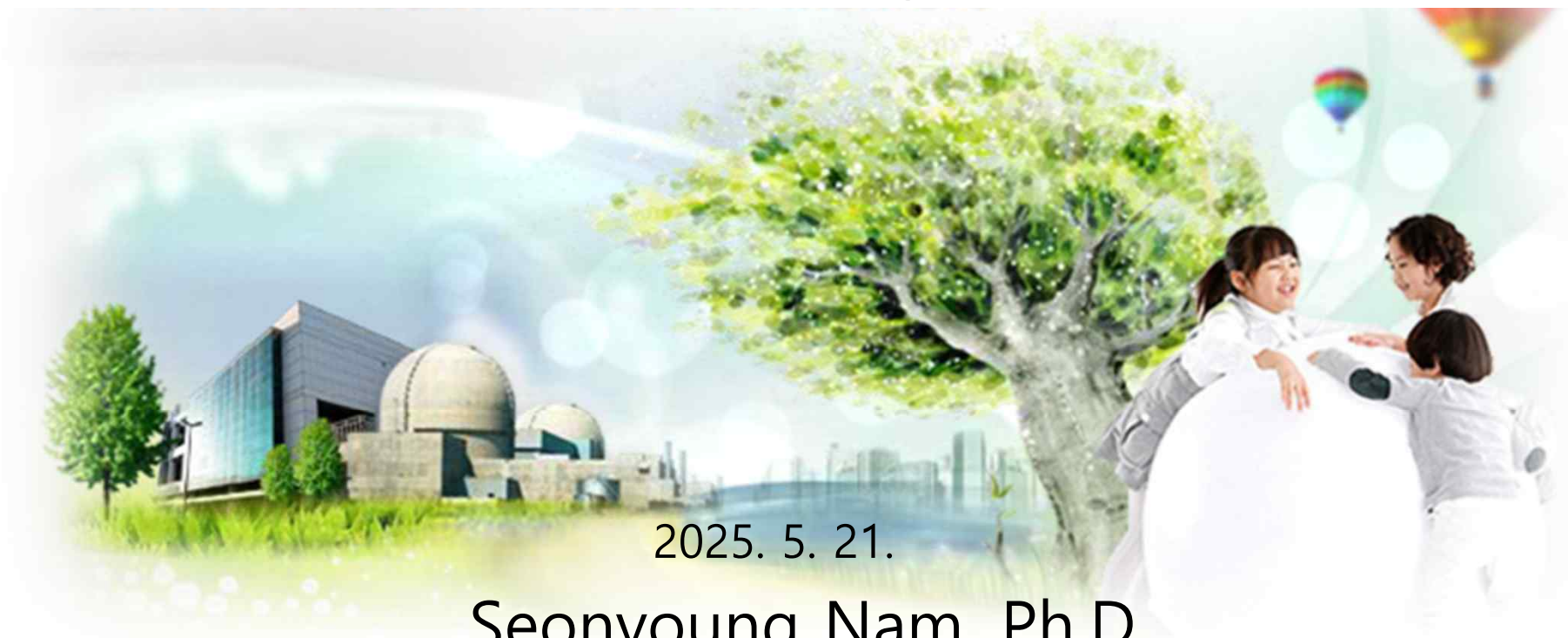


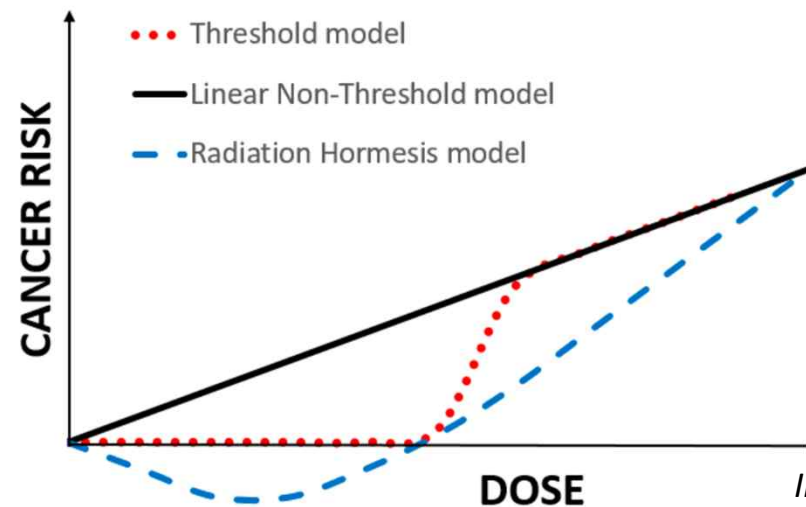
A view on the LNT model based on radiobiological studies



2025. 5. 21.

Seonyoung Nam, Ph.D
Radiation Health Institute, KHNP

Dose-response models for the effects of low dose radiation



Int. J. Mol. Sci. 2020, 21, 6650

It Is Time to Move Beyond the Linear No-Threshold Theory for Low-Radiation Protection

Dose-Response:
An International Journal
July-September 2018:1-24
© The Author(s) 2018



European Heart Journal (2012) 33, 292–295
doi:10.1093/eurheartj/ehz288

EDITORIAL

John J. Cardarelli II¹ and Brant A. Ulsh²



International Journal of
Molecular Sciences

Review

Overview of Biological, Epidemiological Evidence of Radiation Hormesis

Yuta Shibamoto^{1,*} and Hironobu Nakamura^{2,3}

¹ Department of Radiology, Nagoya City University Graduate School of Medicine
Nagoya 467-8601, Japan

Biological effects of low-dose radiation: of harm and hormesis

Tommaso Gori and Thomas Münzel*

Department of Cardiology, University of Cologne, Cologne, Germany

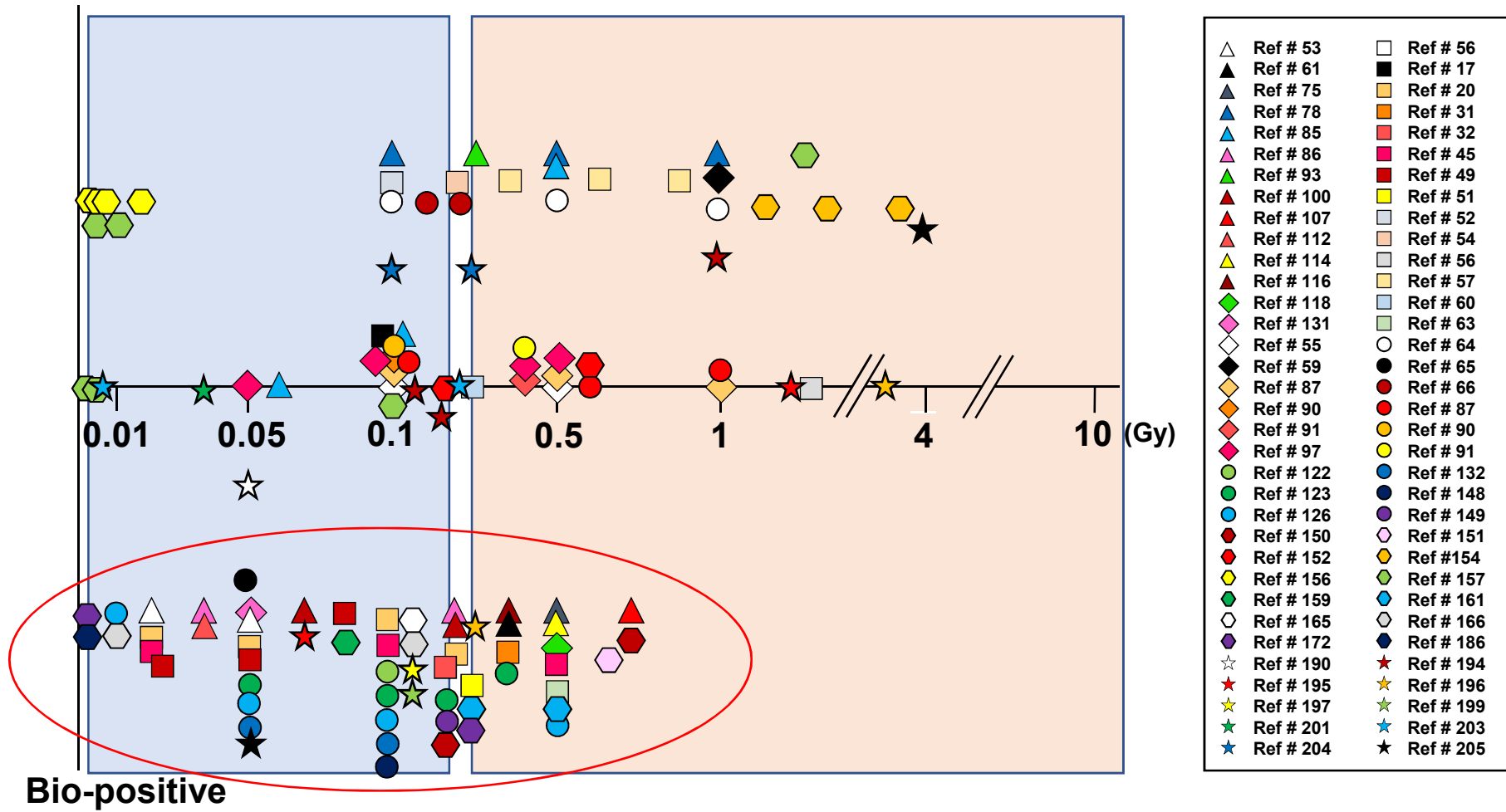
Journal of Environmental Radioactivity 192 (2018) 32–47

Low dose or low dose rate ionizing radiation-induced health effect in the human

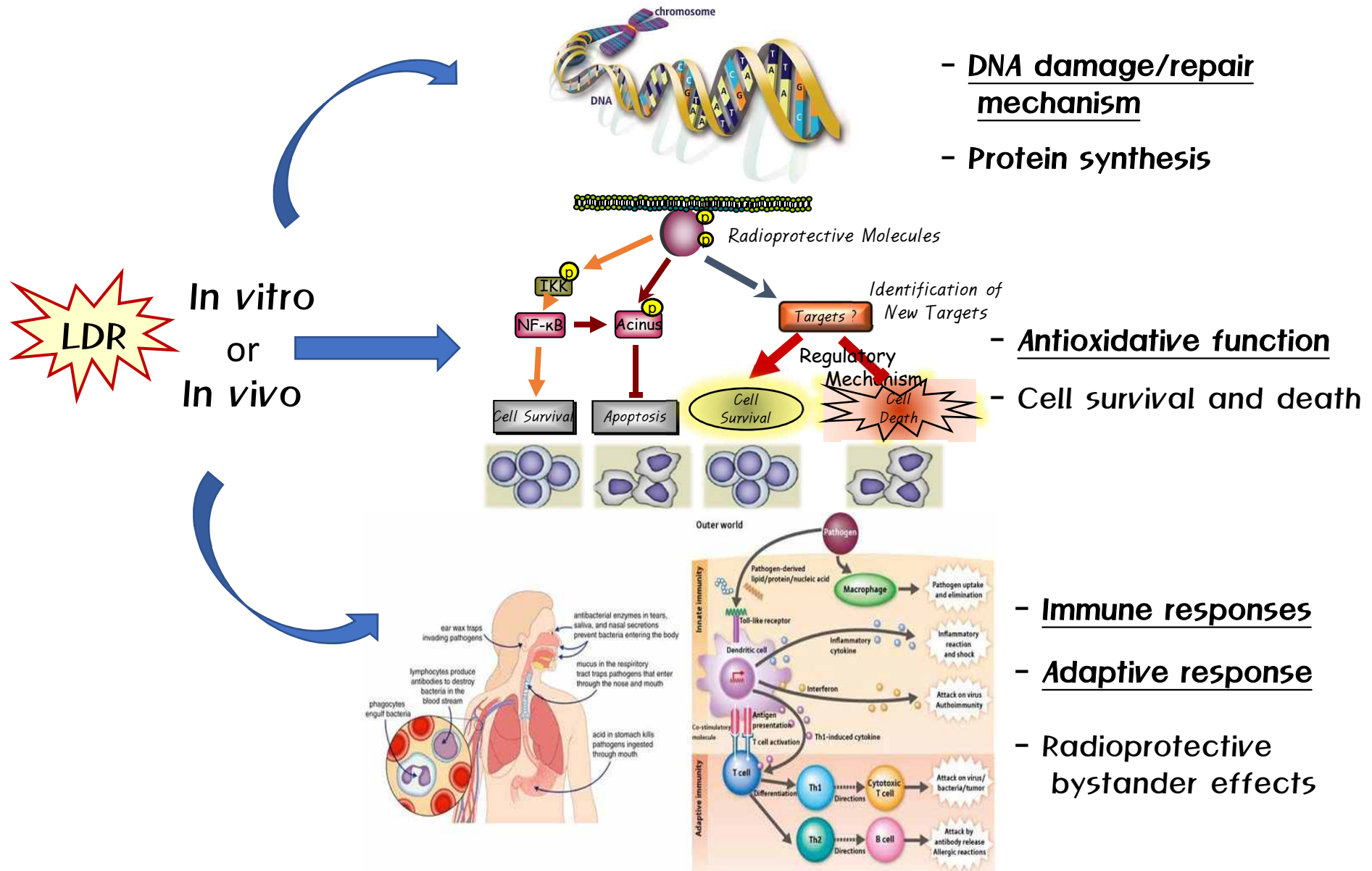
Feng Ru Tang^{a,*}, Konstantin Logunovskiy^b

Radiation effect on biological response (Ref 2011-2018)

Bio-negative



Study on biological response of low dose radiation

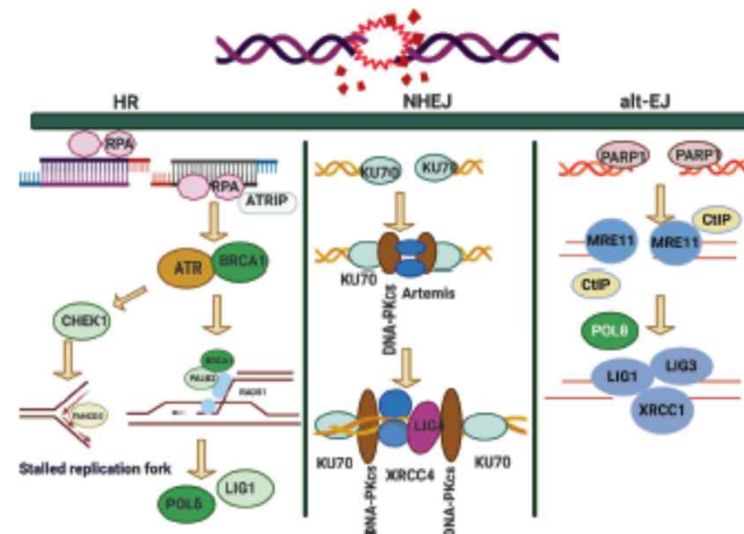
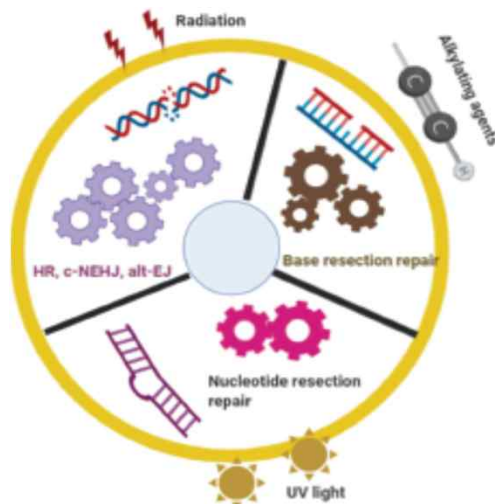


Molecular and Cellular Phenotypes of LDR

DNA damage repair mechanism

- **One million DNA alterations per cell per day** from natural endogenous oxidative metabolism and environmental exposures, **which is efficiently repaired** (Lodish et al., 2004; Branzei et al., 2008; Tharmalingam et al., 2019)
 - 10,000 oxidative damages/cell/day
 - 10,000 apurination or apyrimidination damages/cell/day
 - 55,200 single stranded breaks(SSBs)/cell/day
 - 10~50 double strand breaks(DSB)/cell cycle

“Environmental gear selection” : DNA damage repair pathway evolution



Huang and Zhou, 2021

Molecular and Cellular Phenotypes of LDR

DNA damage repair mechanism

- DNA damage by LDR seems to be cell type and strain specific (*Tubiana et al., 2009; Asaithamby et al., 2009; Rothkamm et al., 2003*)
- DNA damage at a very low dose rate is unnoticeable compared to controls
- Molecular mechanisms utilized by LDR to prevent cells

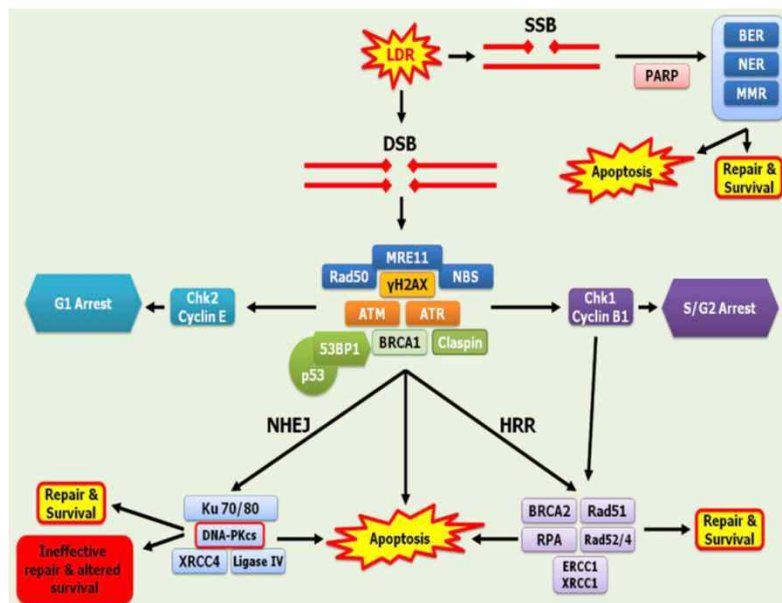


Fig. Repair/removal of LDR induced DNA damage

- Repair of damaged DNA
- Removal of damaged cells via apoptosis
- Cell cycle arrest

(Tharmalingam et al., 2019)

“The ratio of metabolic DNA damage to radiation-induced DNA damage by 1 mGy/year natural background radiation : ~ about 10 million”

Genomic instability : the biological effect of Radiation

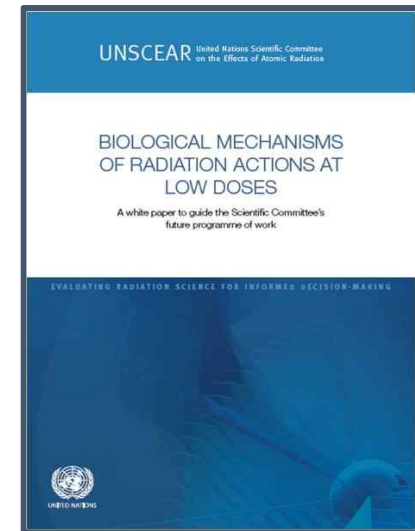
Genomic instability on LDIR is still controversial.

It has been reported that **NO** genomic instability under 100 mGy of radiation.

Dose (mGy)	Cells with abberations	Aberrations/ cell	Chromosome: chromatid aberrations
0	4/908	0.004	3:1
1.7	0/132	0	-
5	1/146	0.007	0:1
12.1	3/346	0.009	0:3
25	0/205	0	-
50	1/464	0.002	1:0
100	3/611	0.006	2:1
500	1/384	0.003	1:0
1000	6/571	0.011	1:5
3000	12/730	0.016	2:10

Cytogenetic aberrations in coded metaphase preparations
obtained from mouse bone marrow 30 days post-irradiation

Radiat. Res. (2011) 175(3):322-327



DNA damage in peripheral blood mononuclear cells of individuals from high level natural radiation areas of Kerala

Jain et al., 2016

- 91 random volunteers
- Level of background radiation :
1.0 mGy/y to 45.0 mGy/y
- gamma-H2AX assay to estimate
DNA DSBs in PBMCs of
individuals

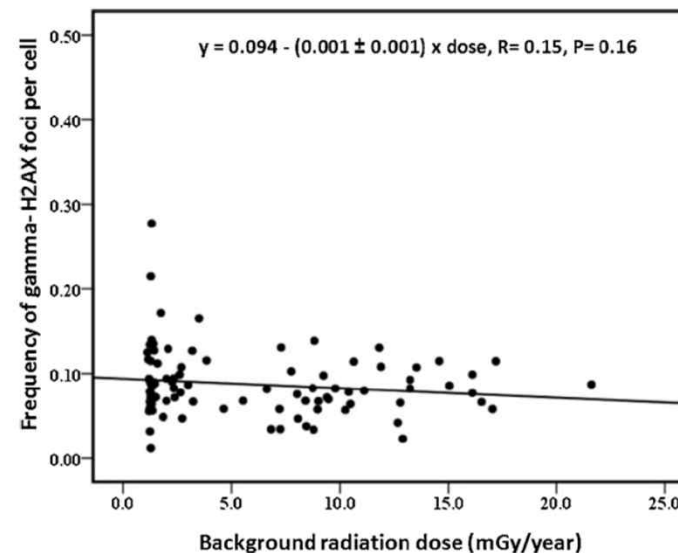


Fig. Distribution of γ -H2AX foci for background radiation dose

Table 1

Distribution of gamma-H2AX foci per cell with respect to age and background dose level among HLNRA and NLNRA individuals. HLNRA: High Level Natural Radiation area, NLNRA: Normal Level Natural Radiation area. LDG: Low Dose group, HDG: High dose group. S. D: standard deviation.

Area	Background dose groups (mGy/year)	Number of individuals studied	Mean Age \pm S.D (Age range in years)	Mean background dose \pm S.D (dose range in mGy/year)	Frequency of gamma-H2AX foci \pm S.E. (range)
NLNRA	≤ 1.50	30	35.5 ± 6.35 (25–50)	1.28 ± 0.086 (1.1–1.50)	0.095 ± 0.009 (0.01–0.28)
HLNRA	LDG (1.51–5.0)	20	34.2 ± 5.7 (25–44)	2.63 ± 0.76 (1.57–4.64)	0.096 ± 0.008 (0.05–0.17)
	HDG (>5.00–21.6)	41	37.1 ± 8.03 (18–59)	11.04 ± 3.57 (5.53–21.60)	0.078 ± 0.004 (0.02–0.14)
HLNRA (Total)	>1.50	61	36.1 ± 7.43 (18–59)	8.28 ± 4.96 (1.57–21.60)	0.084 ± 0.004 (0.02–0.17)

Molecular and Cellular Phenotypes of LDR

Antioxidative function

- **Low dose radiation** stimulates protection from oxidative damage. LDR promotes adaptive responses that **upregulate antioxidative systems** (Scott and Tharmalingam, 2019; Tharmalingam et al., 2019).
- LDR reduced ROS production due to enhanced **expression of antioxidative enzymes** (Nabil et al., 2016).

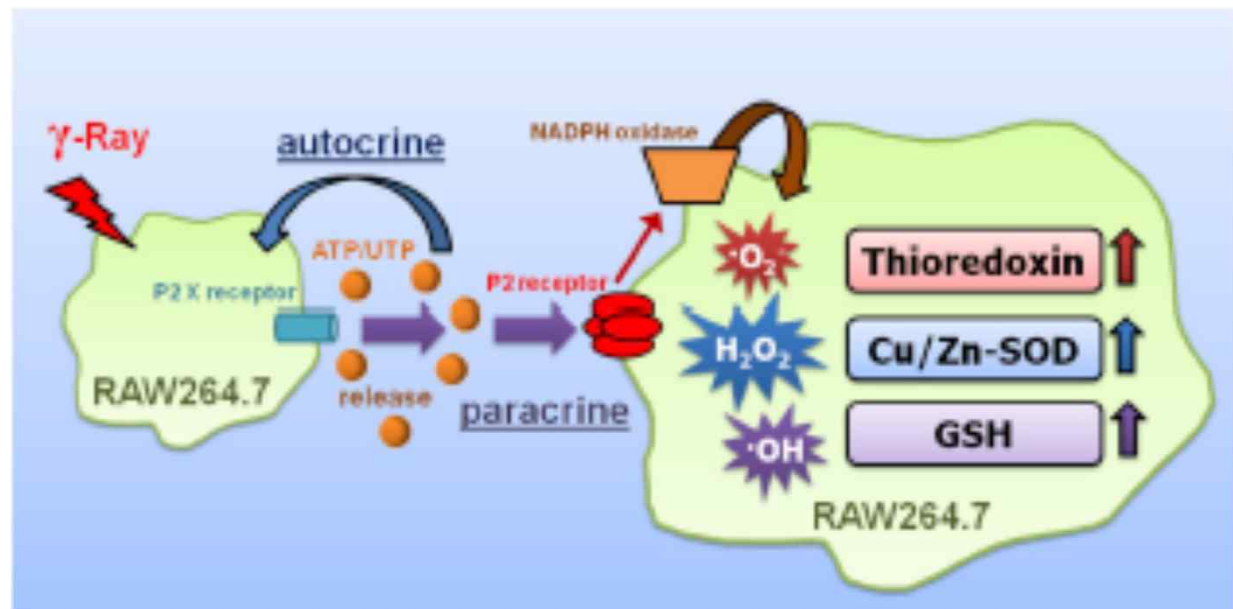


Fig. Model for radiation-induced reactive oxygen species (ROS) production in RAW264.7 cells

(Scott and Tharmalingam, 2019)

SCIENTIFIC REPORTS

OPEN

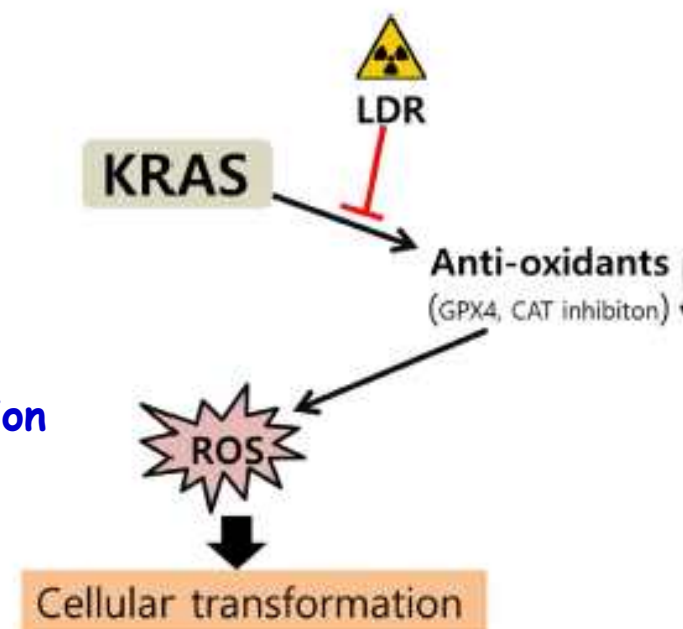
Beneficial effects of low dose radiation in response to the oncogenic KRAS induced cellular transformation

Received: 30 May 2015
Accepted: 22 September 2015
Published: 30 October 2015

Rae-Kwon Kim^{1*}, Min-Jung Kim^{2,*}, Ki Moon Seong^{2,*}, Neha Kaushik¹, Yongjoon Suh¹, Ki-Chun Yoo¹, Yan-Hong Cui¹, Young Woo Jin², Seon Young Nam³ & Su-Jae Lee¹

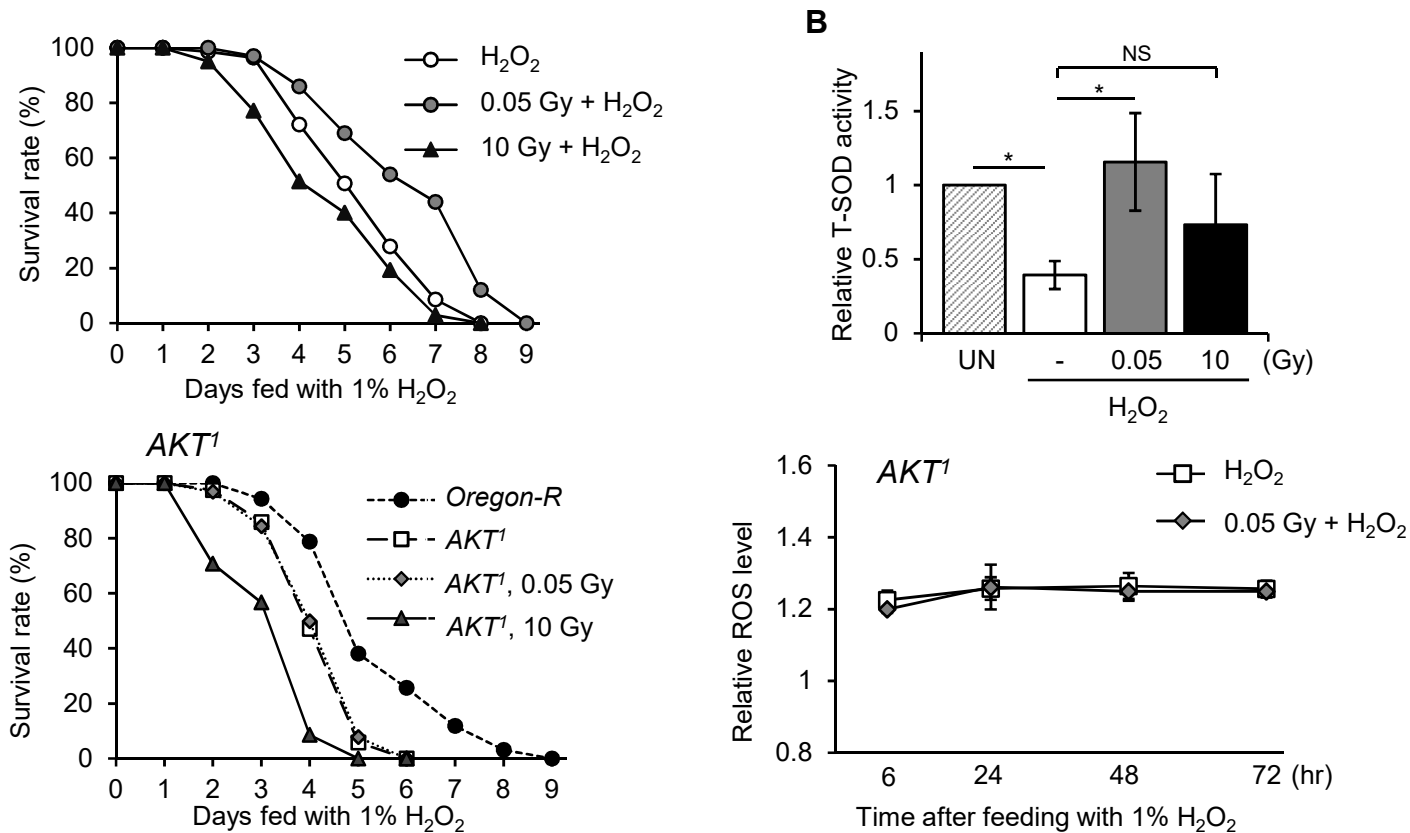
Recently low dose irradiation has gained attention in the field of understanding of the molecular consequences of low dose irradiation concerning its risks on human beings. In this article, we report of blocking the oncogenic *KRAS*-induced malignant transformation we showed that low dose irradiation, at doses of 0.1 Gray (Gy); response against oncogenic *KRAS* -induced malignant transformation the induction of antioxidants without causing cell death and attenuation of reactive oxygen species (ROS). Importantly, we

LDR inhibits KRAS induced cellular transformation via anti-oxidants and ROS regulation



Low-dose radiation increases the lifespan of *Drosophila* under oxidative stress conditions

To be published in IJRB



- **Low-dose ionizing radiation of 0.05 Gy extends the lifespan and survival rates under H₂O₂-induced oxidative stress conditions by controlling ROS levels via AKT activation.**

Molecular and Cellular Phenotypes of LDR

Adaptive response : Cell survival

- **Low-dose radiation** stimulates selective **apoptosis of neoplastic transformed cells**. Thus, the dose-response relationship for neoplastic transformation has been found to be **hormetic** (*Bauer, 2011*).
- The reduction in transformation relative risk (RR) at low doses is related to the **protective processes (ex, DNA damage repair and apoptosis of transformed cells)** that operate at the molecular, cellular, and tissue levels (*Bauer, 2007*).
- The LNT model for cancer induction is not supported by radiobiological data (*Scott and Tharmalingam, 2019*)

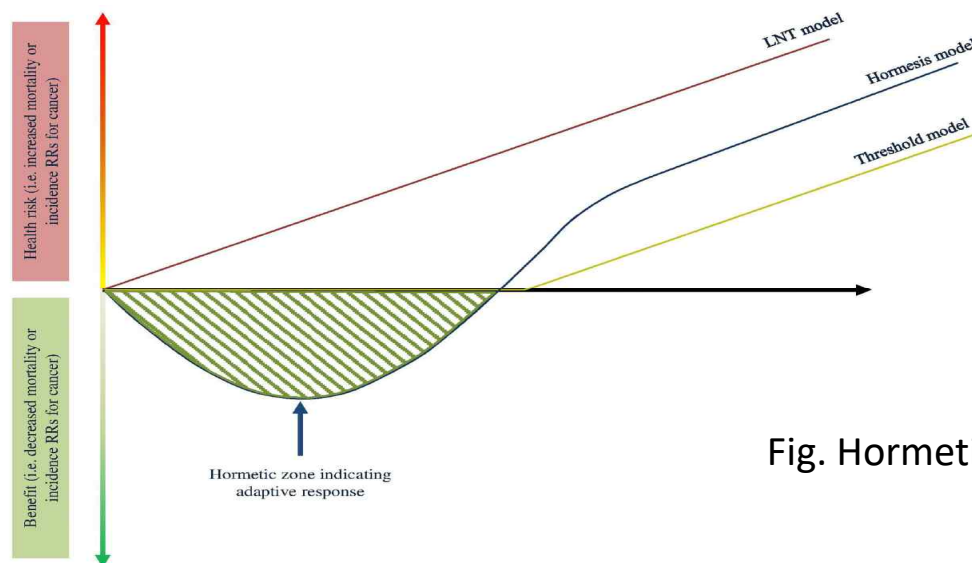


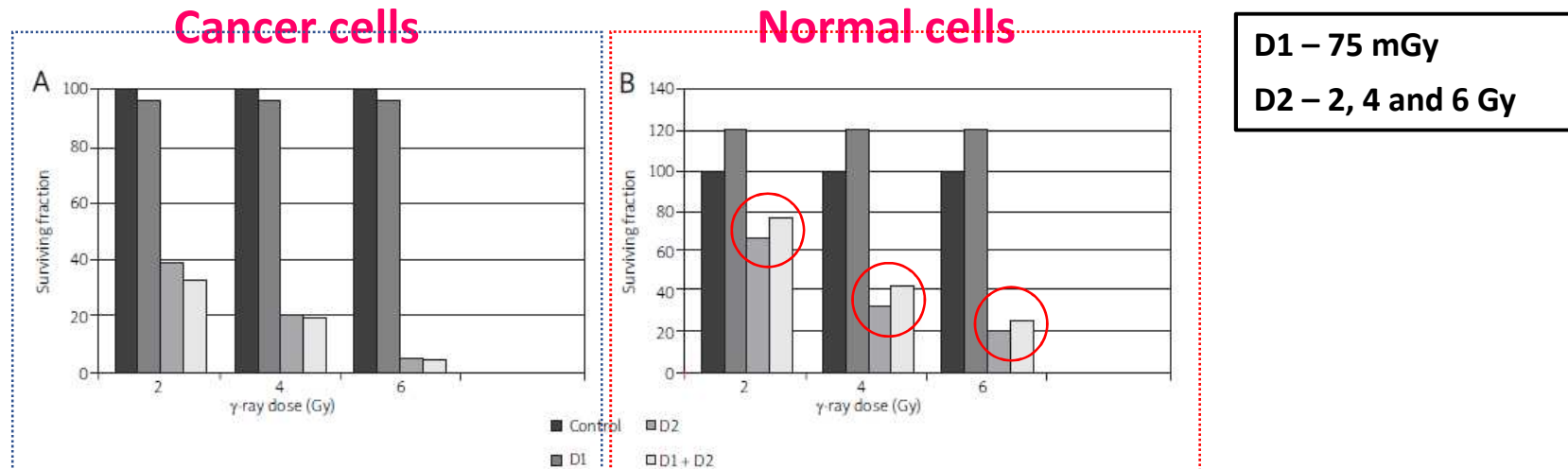
Fig. Hormetic model for radiation risk

(Iavicoli et al., 2023)

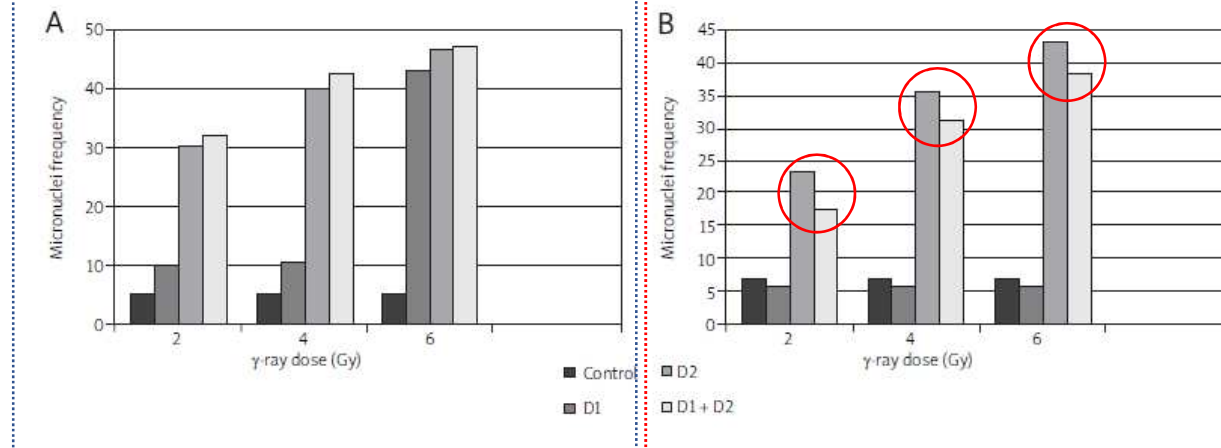
Different responses of tumor and normal cells to low-dose radiation

Yu et al., *Contemp Oncol(Pozn)*, 2013

Cell survival

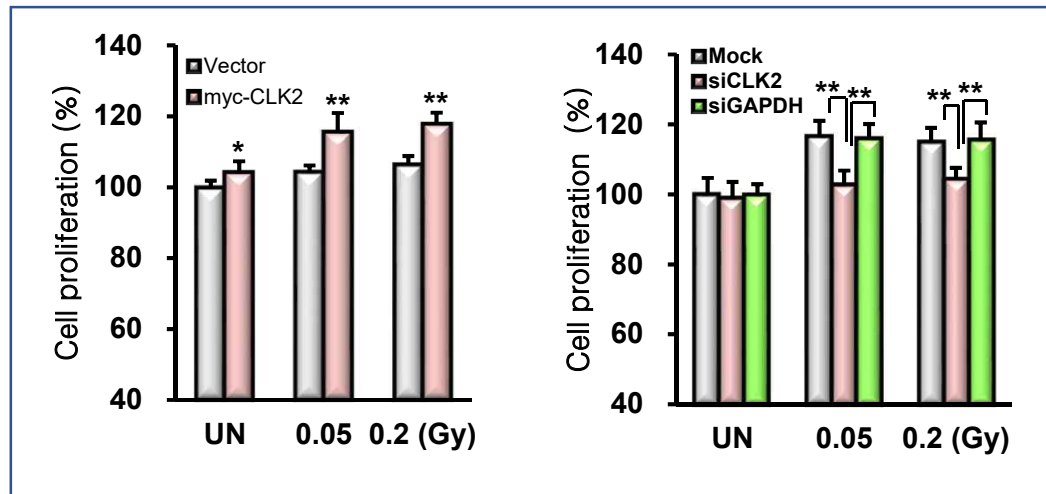
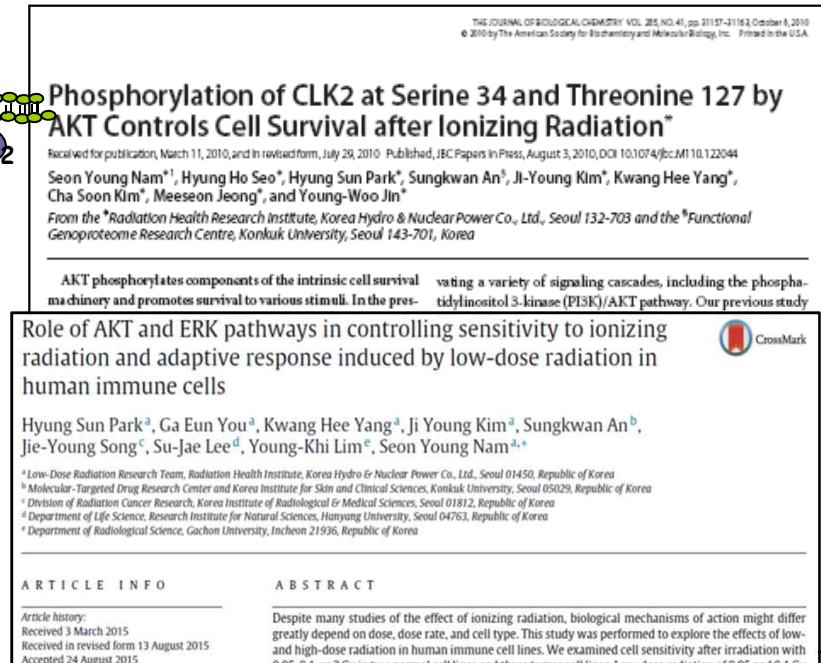
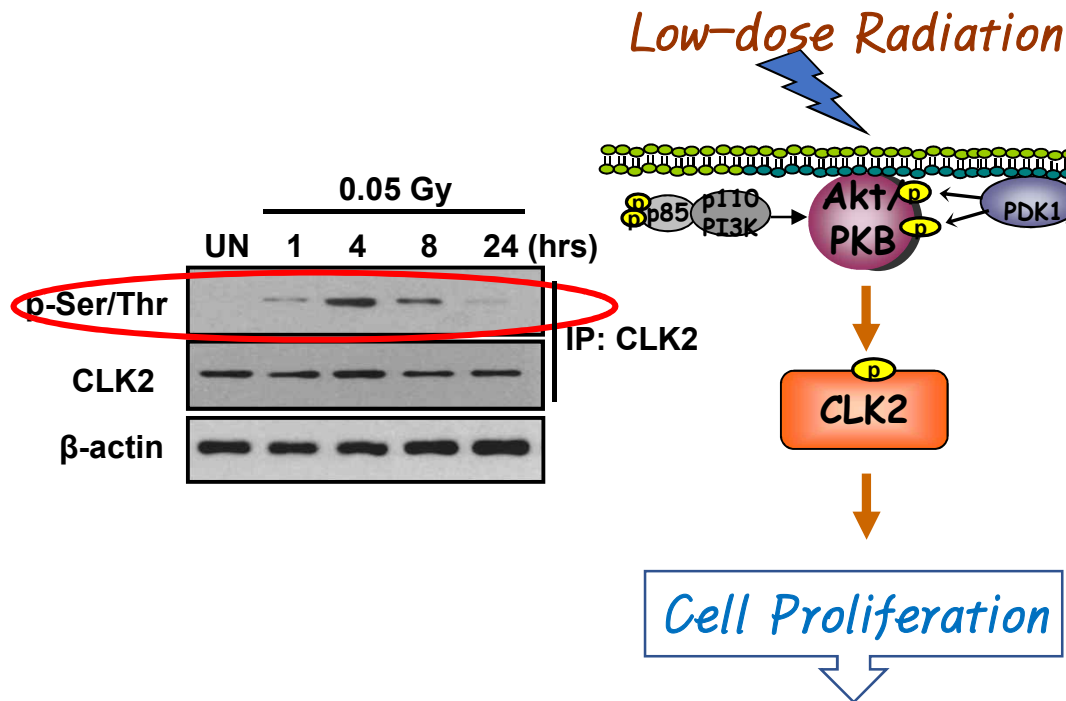


DNA damage



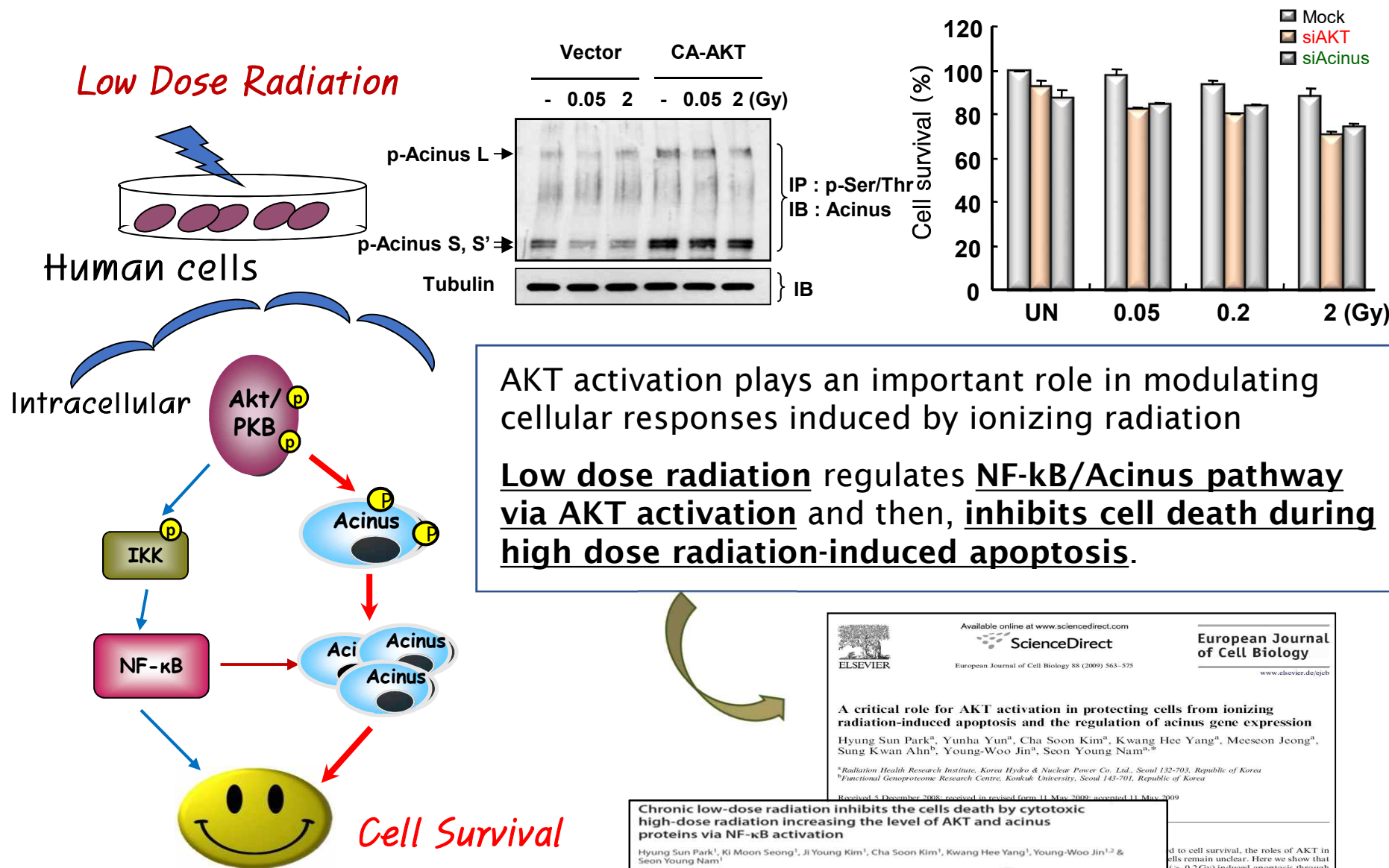
**Normal cell specific
adaptive response!**

Low-dose radiation promotes cell proliferation

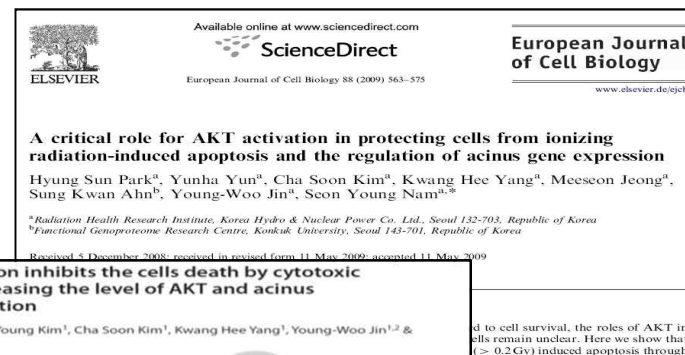


- Low-dose radiation induces **CLK2 phosphorylation via AKT activation** and promotes cell survival
- In normal cells lacking basal AKT activity, chronic low-dose radiation increases activation of the **ERK pathway**, which plays an important role in the **adaptive response** to radiation.

Ionizing radiation activates cell protective molecules



Nam et al., EJC, 2009; IJR, 2013



Chronic low-dose radiation inhibits the cells death by cytotoxic high-dose radiation increasing the level of AKT and acinus proteins via NF-κB activation

Hyung Sun Park¹, Ki Moon Seong¹, Ji Young Kim¹, Cha Soon Kim¹, Kwang Hee Yang¹, Young-Woo Jin^{1,2} & Seon Young Nam¹

¹Radiation Health Research Institute, Korea Hydro & Nuclear Power Co., Ltd, Seoul, Korea, and ²Department of Planning & Research for Radiological Emergency, National Radiation Emergency Medical Center, Korea Institute of Radiological & Medical Sciences, Republic of Korea

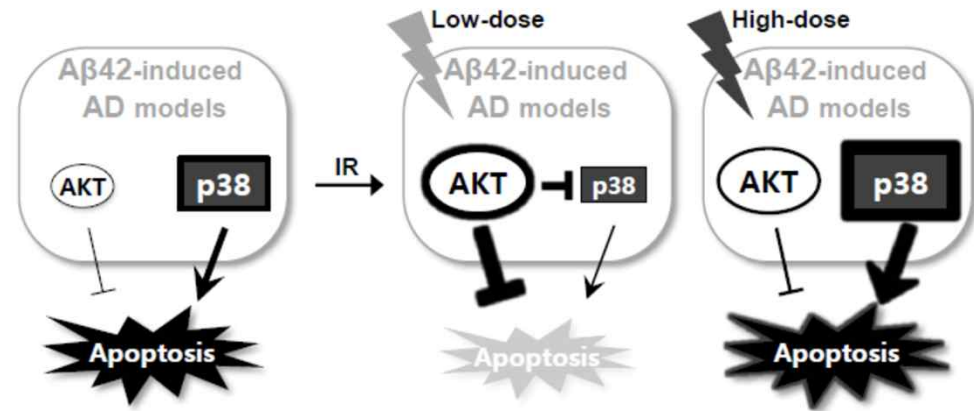
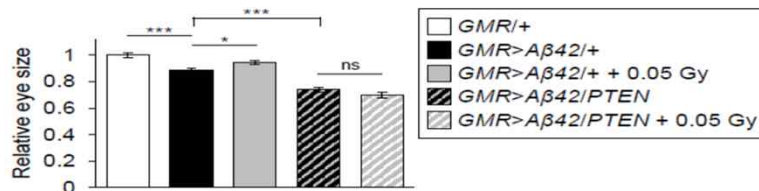
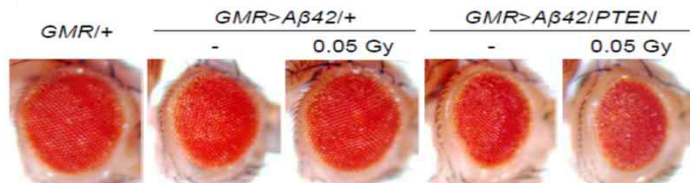
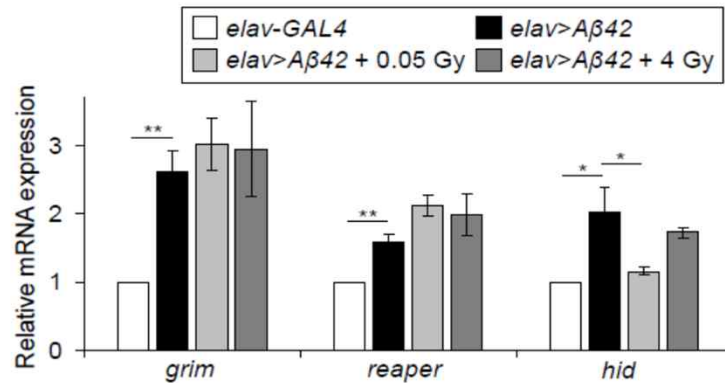
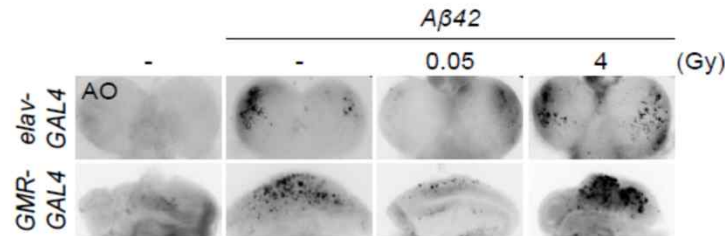
Abstract

Purpose: This study explored the effects of low-dose and low-dose-rate irradiation in human lung fibroblast CCD-18Lu cells

arrest, apoptosis, and carcinogenesis (Di Pietro et al. 1996, Krasnikov et al. 1999, Choi et al. 2007, Portess et al. 2007, Wang et al. 2007). Low-dose ionizing radiation has been observed

to cell survival, the roles of AKT in cells remain unclear. Here we show that (> 0.2 Gy) induced apoptosis through

The effects of low-dose radiation in *in vivo* models



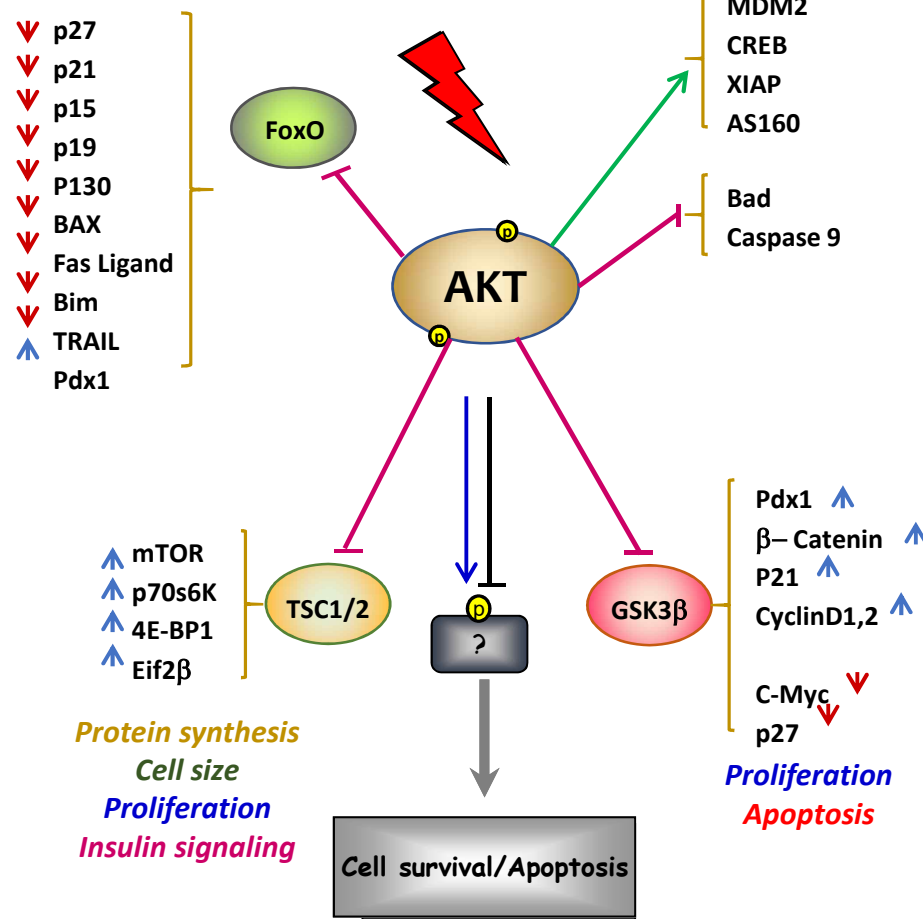
- Chronic low-dose γ -irradiation of *Drosophila melanogaster* larvae induces gene expression changes and enhances locomotive behavior
- **Low-dose radiation alleviates *Aβ42*-induced cell death via regulating AKT and p38 pathways in *Drosophila* Alzheimer's disease models**

Adaptive responses by LDR and related molecular changes

Proliferation

Apoptosis

Senescence



Dose-Response 4(2):75-90, 2006
Formerly Nonlinearity in Biology, Toxicology, and Medicine
Copyright © 2006 University of Massachusetts
ISSN: 1559-3258
DOI: 10.2203/dose-response.04-002.Mitchel

International Hormesis Society
www.hormesisociety.org

LOW DOSES OF RADIATION ARE PROTECTIVE *IN VITRO* AND *IN VIVO*: EVOLUTIONARY ORIGINS

J. Radiat. Res., 49, 219-230 (2008)

Regular Paper

Low-Dose Radiation Induces Adaptive Response in Normal Cells, but not in Tumor Cells: *In vitro* and *in vivo* Studies

Hongyu JIANG¹, Wei LI¹, Xiuyi LI², Lu CAI^{1,2,3*} and Guanjun WANG^{1,2*}

Journal of Radiation Research, Vol. 0, No. 0, 2015, pp. 1-10
doi: 10.1093/jrr/cru128
Regular Paper

Journal of
Radiation
Research
OXFORD

Chronic low-dose γ -irradiation of *Drosophila melanogaster* larvae induces gene expression changes and enhances locomotive behavior

Cha Soon Kim¹, Ki Moon Seong², Byung Sub Lee¹, In Kyung Lee¹, Kwang Hee Yang¹, Ji-Young Kim¹ and Seon Young Nam^{1,*}

¹Low-dose Radiation Research Team, Radiation Health Institute, Korea Hydro and Nuclear Power Co. Ltd, Seoul 132-703, Korea
²National Radiation Emergency Medical Center, Korea Institute of Radiological and Medical Sciences, Seoul 139-736, Korea
^{*}Corresponding author. Tel: +82-2-3499-6660; Fax: +82-2-3499-6669; Email: syanam0605@khnp.co.kr
Received August 11, 2014; Revised December 15, 2014; Accepted December 27, 2014

ABSTRACT

Although radiation effects have been extensively studied, the biological effects of low-dose radiation (LDR) are controversial. This study investigates LDR-induced alterations in locomotive behavior and gene expression profiles of *Drosophila melanogaster*. We measured locomotive behavior using larval pupation height and the rapid iterative negative geotaxis (RING) assay after exposure to 0.1 Gy γ -radiation (dose rate of 16.7 mGy/h). We also observed

Low-dose of Ionizing Radiation Enhances Cell Proliferation Via Transient ERK1/2 and p38 Activation in Normal Human Lung Fibroblasts

Cha Soon KIM^{1,2}, Jin-Mo KIM^{1,3}, Seon Young NAM¹, Kwang Hee YANG¹,

Int J Radiat Biol. 2012 Oct;88(10):727-34. Epub 2012 May 22.

Low dose ionising radiation leads to a NF- κ B dependent decreased secretion of active IL-1 β by activated macrophages with a discontinuous dose-dependency.

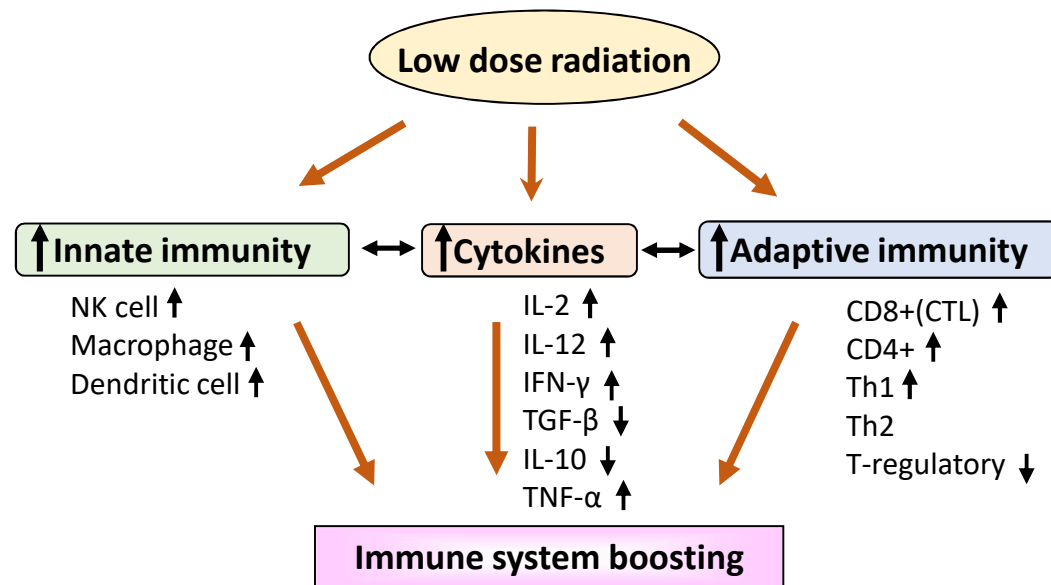
Lödermann B, Wunderlich R, Frey S, Schorn C, Stanol S, Rödel F, Keilholz L, Fietkau R, Gajol US, Frey B.

Department of Radiation Oncology,

Molecular and Cellular Phenotypes of LDR

Immunological activity

- **Low radiation doses** and dose rates can **attenuate an ongoing inflammatory process** and this strategy has been used in treating inflammatory and degenerative diseases (*Frey et al., 2015*).
- LDR leads **to immune system boosting and local tumor control** (*B. R. Scott and S. Tharmalingam, 2019*).



- While high doses of radiation suppress the immune system, low doses and dose rates can **stimulate anticancer immunity** which can aid in cancer prevention (*Liu et al., 2007; Liu, 2003; Ren, et al., 2006; Janiak et al., 2017*).

Immune system components modulation by LDR

Transcriptome analysis of low-dose ionizing radiation-impacted genes in CD4+ T-cells undergoing activation and regulation of their expression of select cytokines

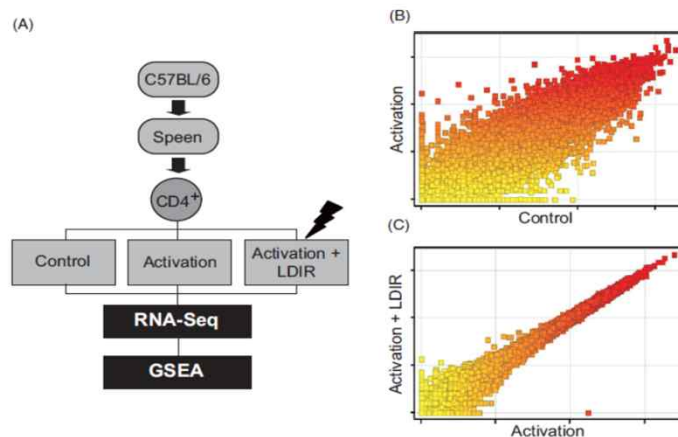


Fig. Overview of transcriptome analysis

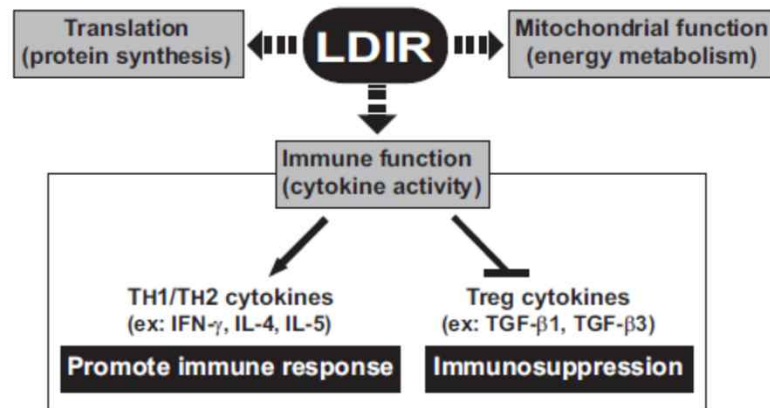


Fig. Model for LDIR-regulated cellular functions

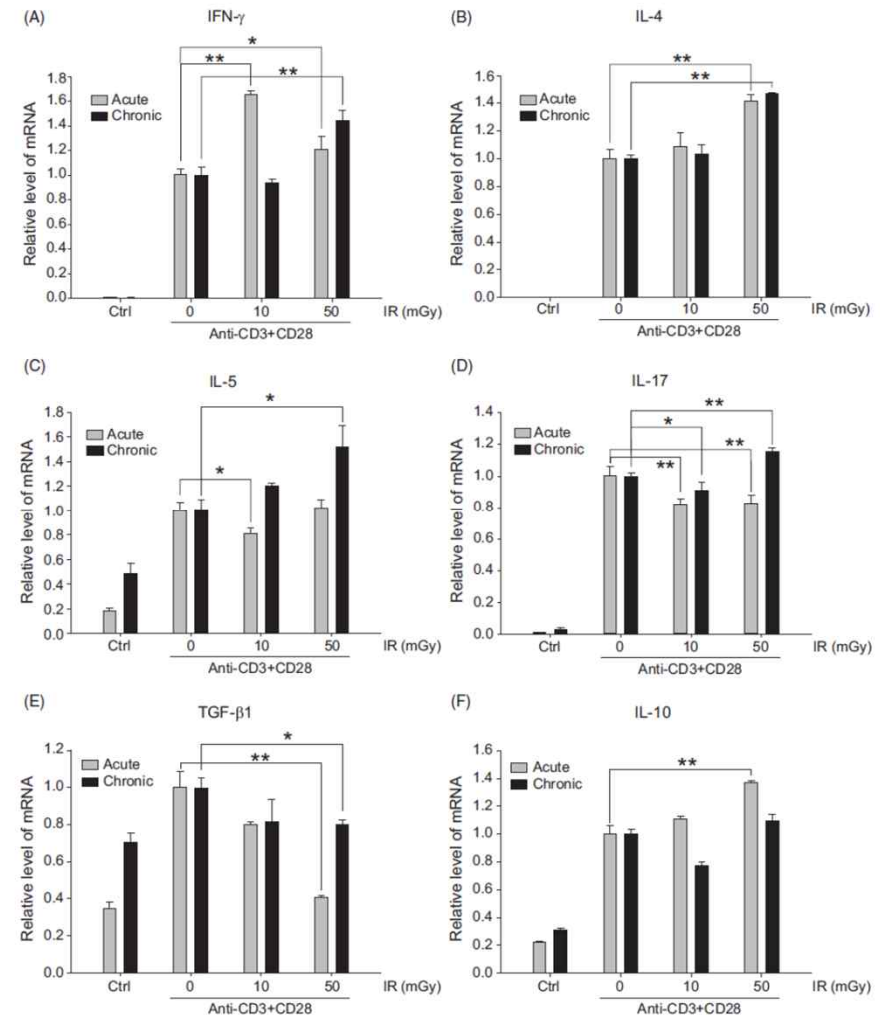


Fig. LDIR effects on cytokine gene expression in CD4⁺ T-cells undergoing activation.

The effects of low-dose radiation in immunological activity



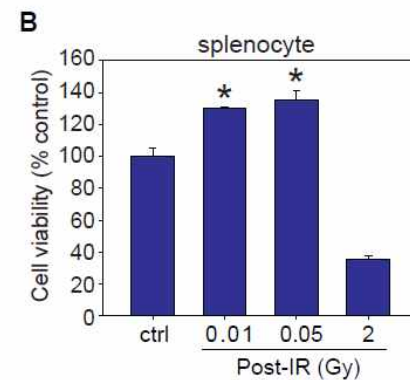
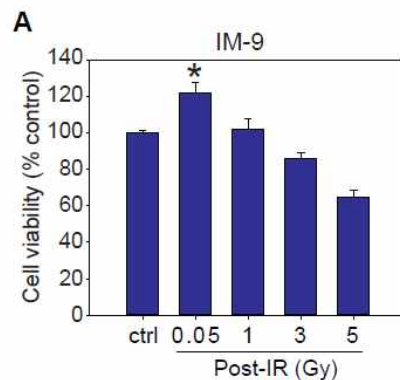
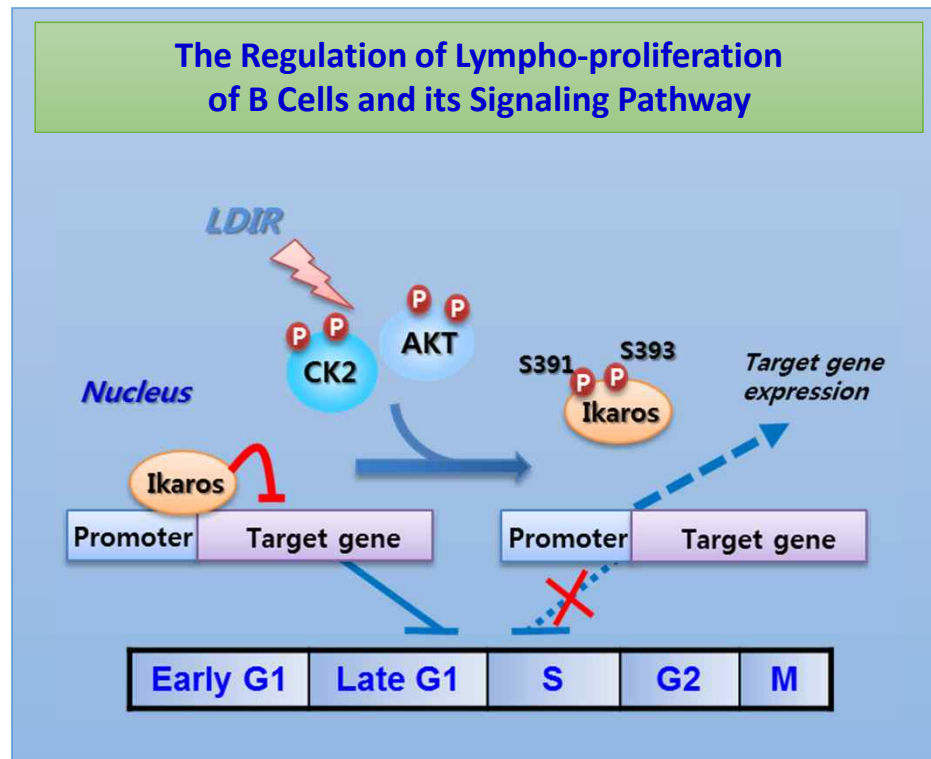
Biology Contribution

Site-Specific Phosphorylation of Ikaros Induced by Low-Dose Ionizing Radiation Regulates Cell Cycle Progression of B Lymphoblast Through CK2 and AKT Activation

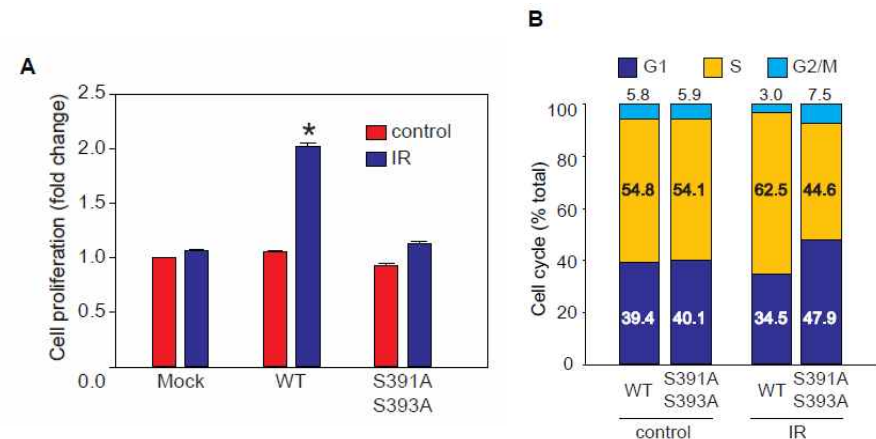
Seong-Jun Cho, PhD,* Hana Kang, MS,* Min Young Kim, MS,[†]
Jung Eun Lee, PhD,* Sung Jin Kim, MS,* Seon Young Nam, PhD,*
Ji Young Kim, PhD,* Hee Sun Kim, PhD,* Suhkneung Pyo, PhD,[‡]
and Kwang Hee Yang, PhD*

*KHNP Radiation Health Institute, Korea Hydro & Nuclear Power Co, Seoul, South Korea;
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Received Oct 29, 2015, and in revised form Dec 30, 2015. Accepted for publication Jan 6, 2016.

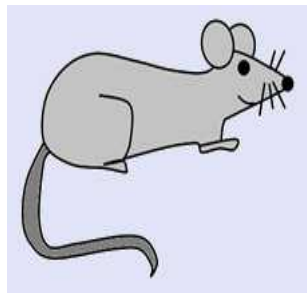
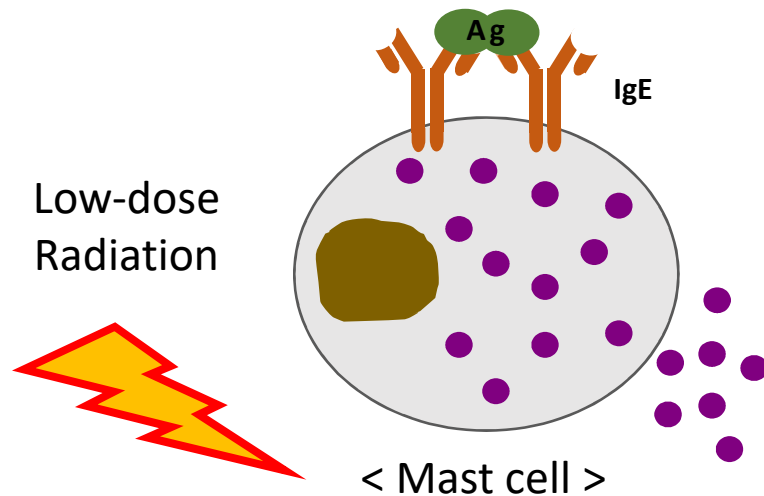


LDIR increases cell proliferation of B lymphoblast and splenocytes.



LDIR-specific phosphorylation regulates cell proliferation and cell cycle progression of B cells

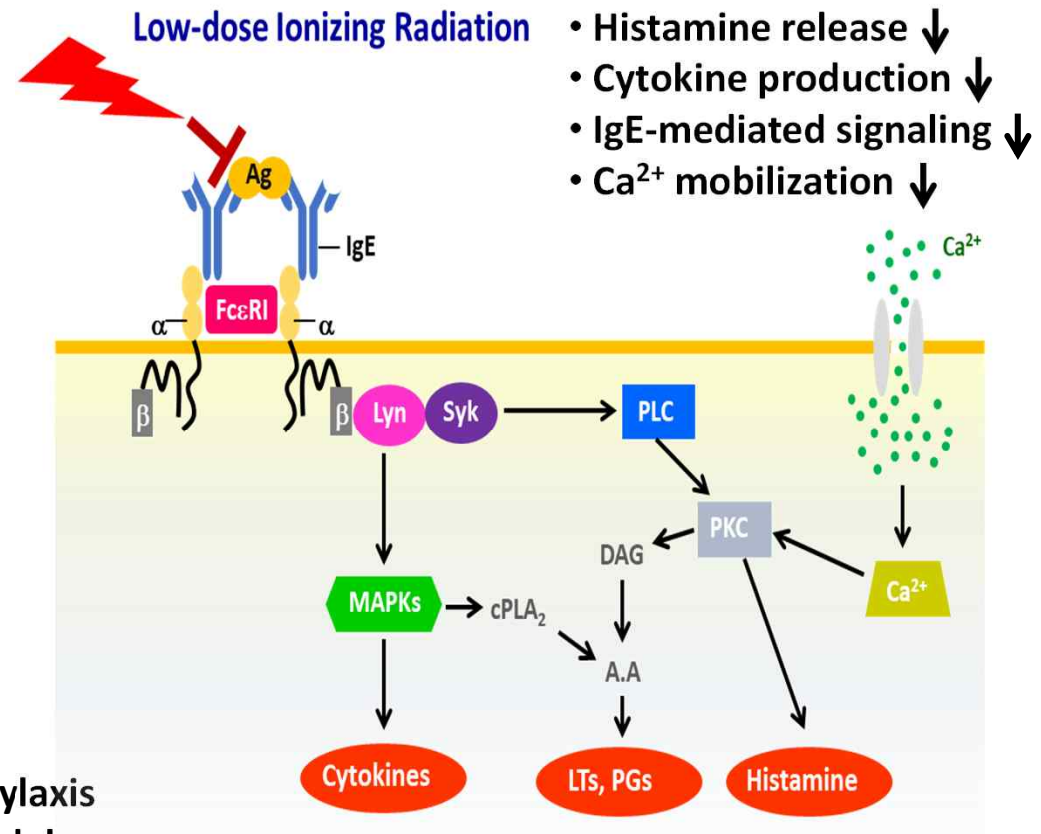
Effects of low-dose radiation on the allergic response



- IgE-mediated passive cutaneous anaphylaxis
- IgE-mediated late-phase cutaneous model

< Mouse model >

➡ Allergic Response Inhibition



The effects of low-dose radiation on rheumatoid arthritis

Journal of Radiation Research, Vol. 65, No. 2, 2024, pp. 177–186
https://doi.org/10.1093/jrr/rrad101
Advance Access Publication: 28 December 2023



Preventive and therapeutic effects of low-dose whole-body irradiation on collagen-induced rheumatoid arthritis in mice

Ji Young Kim^{1,*}, Yeong Ro Lee¹, Young Ae Lee¹, Chin-Hee Song¹, So Hyun Han¹, Seong Jun Cho¹ and Seon Young Nam²

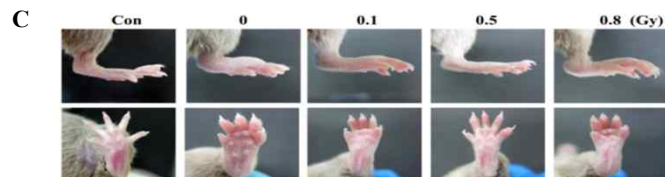
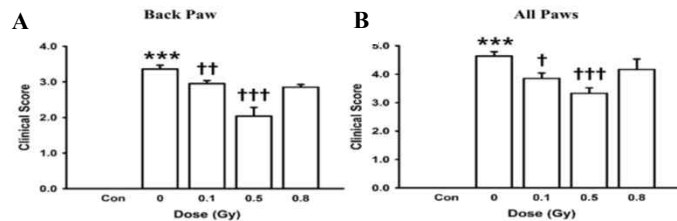
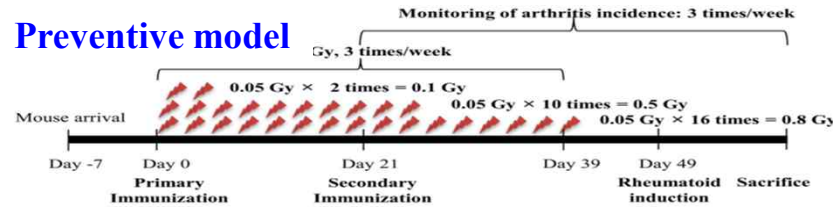
¹Radiation Effects Research Section, Radiation Health Institute, Korea Hydro & Nuclear Power Co., Ltd., Seoul 04505, Republic of Korea

²R&D Strategy & Planning Section, Radiation Health Institute, Korea Hydro & Nuclear Power Co., Ltd., Seoul 04505, Republic of Korea

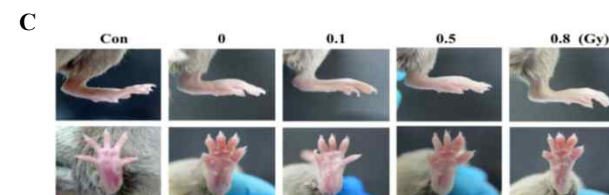
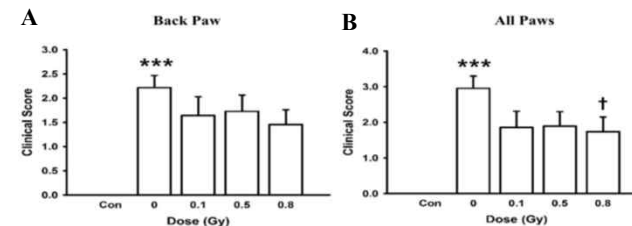
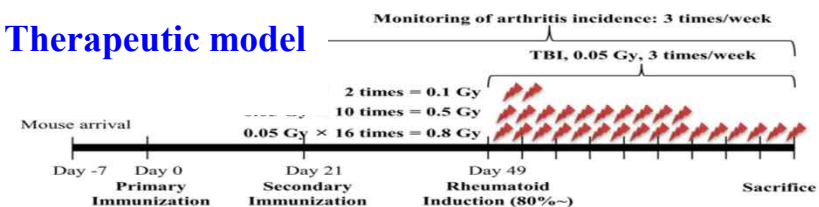
*Corresponding author. Radiation Effects Research Section, Radiation Health Institute, Korea Hydro & Nuclear Power Co., Ltd., 38 Seosomun-ro Jung-gu, Seoul 04505, Republic of Korea. Tel: +82-2-61-06-44-10; Fax: +82-5-02-73-40-56-0; Email: elizabeth@khnp.co.kr
(Received 8 April 2023; revised 29 August 2023; editorial decision 24 November 2023)

- Preventive effects : IgG↓,
inflammatory cytokines(IL-1β, TNF-α,)↓
Clinical score↓, Incidence↓
- Therapeutic effects : IgG↓,
inflammatory cytokines(IL-1β, IL-6)↓
Clinical score↓

Preventive model

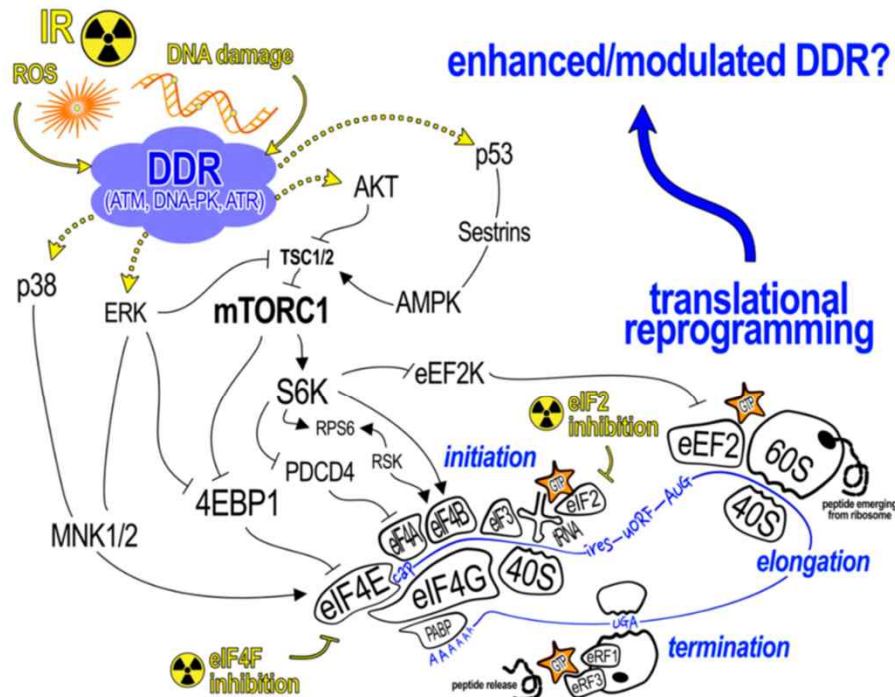


Therapeutic model



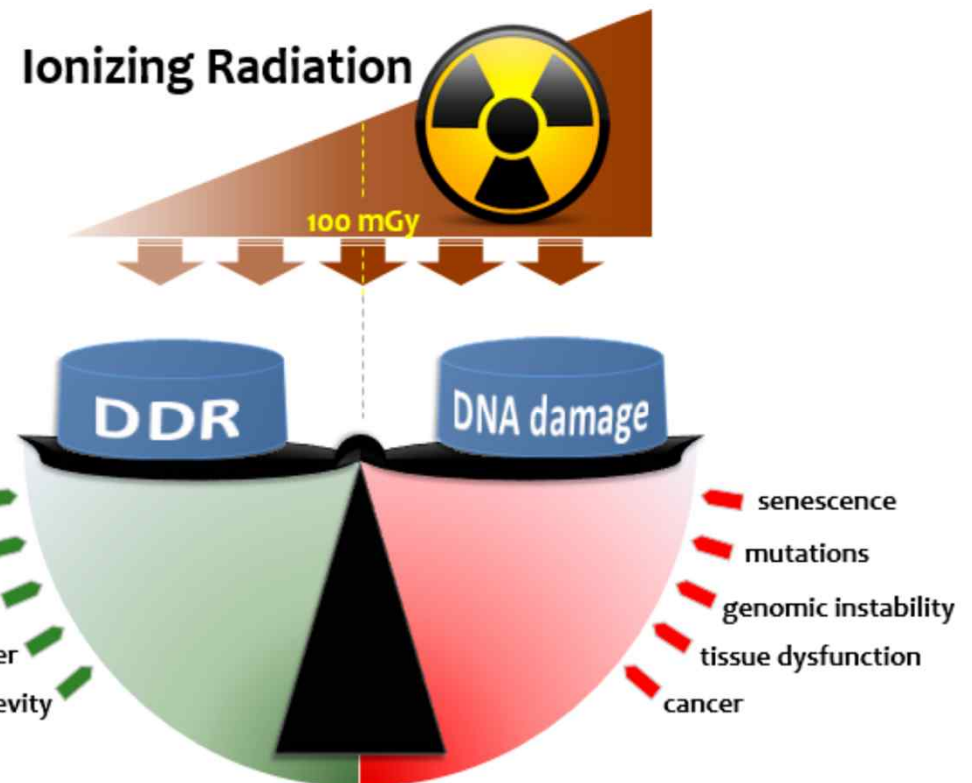
Low Dose Radiation : A Link to Radiation Hormesis?

Kabilan et al., Int. J. Mol. Sci., 2020



Low Dose Radiation:

- *de novo* protein synthesis
- translational reprogramming
- DNA damage signaling control
- Radiation hormesis phenotype



Clinical Trials : Therapeutic potential of LDR against cancer, dementia, and diabetes

Journal of Alzheimer's Disease 80 (2021) 1119–1128
DOI 10.3233/JAD-200620
IOS Press

Low Doses of Ionizing Radiation as a Treatment for Alzheimer's Disease: A Pilot Study

Jerry M. Cuttler^a, Eslam Abdellah^b, Yael Goldberg^b, Sarmad Al-Shamaa^b, Sean P. Symo Sandra E. Black^{c,f,g} and Morris Freedman^{b,g,h,i,*}
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Alzheimer's Disease: Possible Mechanisms Behind Neurohormesis Induced by Exposure to Low Doses of Ionizing Radiation

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ABSTRACT

In 2016, scientists reported that human exposure to low doses of ionizing radiation (CT scans of the brain) might relieve symptoms of both Alzheimer's disease (AD) and Parkinson disease (PD). The findings were unbelievable for those who were not familiar with the concept of neurohormesis.

Therapeutic potential of low dose ionizing radiation against cancer, dementia, and diabetes: evidences from epidemiological, clinical, and preclinical studies

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Received: 22 June 2022 / Accepted: 14 December 2022 / Published online: 3 January 2023
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Abstract

The growing use of ionizing radiation (IR)-based diagnostic and treatment methods has been linked to increasing chronic diseases among patients and healthcare professionals. However, multiple factors such as IR dose, dose-rate, and duration of exposure influence the IR-induced chronic effects. The predicted links between low-dose ionizing radiation (LDIR) and health risks are controversial due to the non-availability of direct human studies. The studies pertaining to LDIR effects have importance in public health as exposure to background LDIR is routine. It has been anticipated that data from epidemiological and clinical reports and results of preclinical studies can resolve this controversy and help to clarify the notion of

Update on a Patient With Alzheimer Disease Treated With CT Scans

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This letter updates the April 2016 case report¹ about an 81-year-old patient who was in the final stages of advanced Alzheimer disease (AD) in hospice care. A neuropsychologist examined her on May 21, 2015, and concluded that she was "completely nonresponsive." Following treatment by 4 computed tomography (CT) scans of the brain from July to August 2015, the patient made a remarkable recovery. A fifth scan on October 1 caused a setback, from which she gradually recovered. On November 20, she was judged to be no longer eligible for hospice care because her condition was sufficiently improved. Since then, she has participated in a stimulating, dementia day care program. Photos on December 14, 2015, Figures 1 and 2, demonstrate restoration of appetite and responsiveness.

Recognizing that the efficacy of the CT scan treatments would likely be transitory, the patient's spouse requested ongoing booster scans every 4 to 5 months. These started on February 24, 2016, about 21 weeks after the October 1 treatment.

Dr William D. MacInnes (note 1) reexamined the patient on April 15, 2016. His progress note states:

Unlike our last visit, Mrs XXX was able to give simple verbal responses to direct, simple questions. Not all of her responses were related to the direct questions, but she seemed to be reacting appropriately to the prosody and nonverbal cues of those


Dose-Response:
An International Journal
January-March 2017;1-2
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DOI: 10.1177/1559325817693167
journals.sagepub.com/home/dos


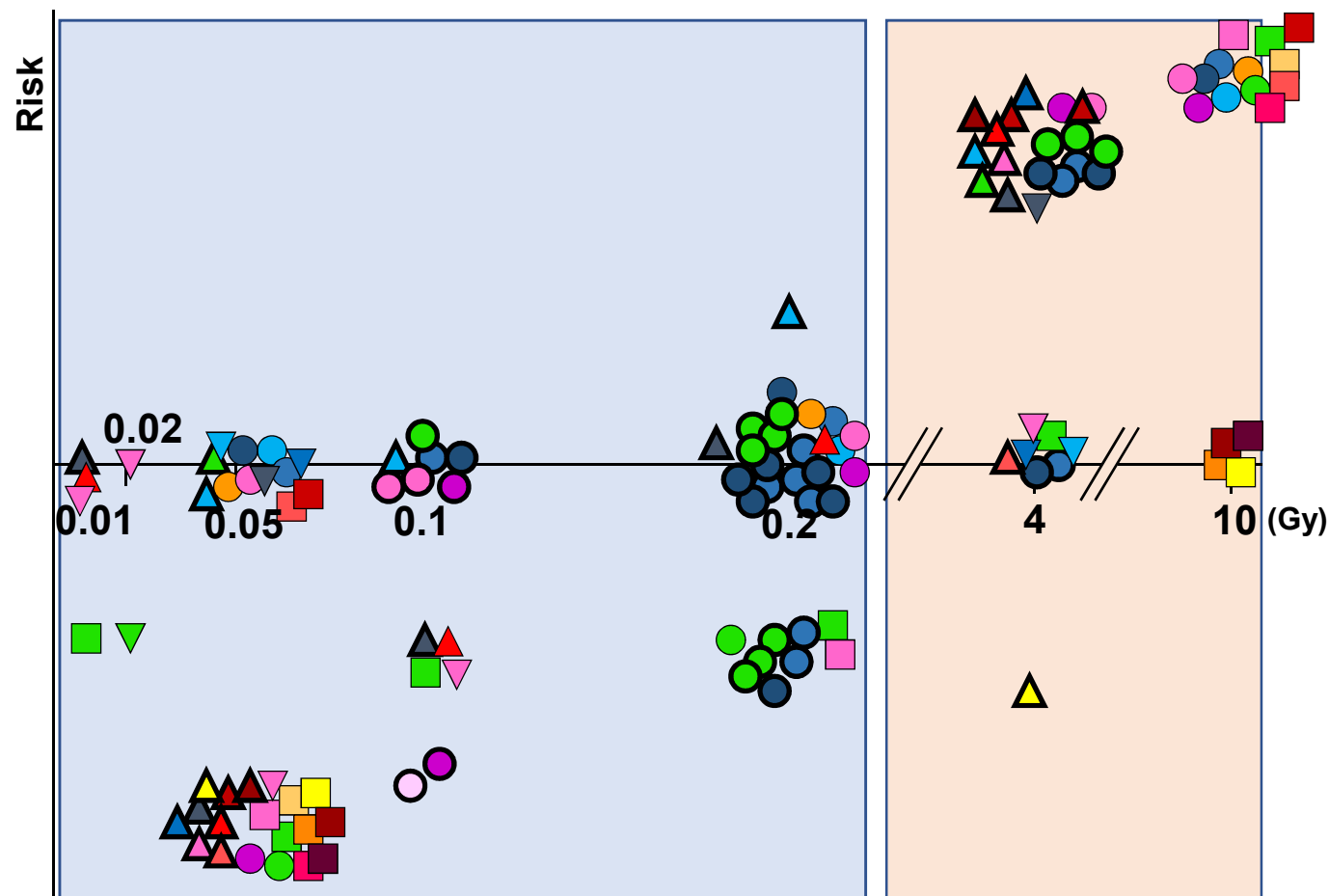


Fig. Restoration of appetite of patient with Alzheimer disease(AD)

Summary : Biological response of radiation dose

Drosophila in vivo models

Bio-negative



Bio-positive

○ △, Published; □, To be published

- Alzheimer model
 - ▲ Development-eye¹
 - ▲ Development-wing¹
 - ▲ Development-hatching¹
 - ▲ Locomotion¹
 - ▲ Lifespan¹
 - ▲ Apoptosis inh-brain¹
 - ▲ Apoptosis inh-eye¹
 - ▲ Apoptosis inh-hid¹
 - ▲ Survival signal-Akt¹
 - ▲ Death signal-p38¹
- Oxidative stress model
 - Survival rate
 - Locomotion
 - ROS-level
 - ROS-SOD activity
 - Apoptosis inh-grim
 - Apoptosis inh-reaper
 - Apoptosis inh-hid
 - Survival signal-Akt
 - Death signal-p38
 - Death signal-JNK
- Wild type
 - Development-hatching
 - Development-pupation⁵
 - Development-eclosion⁵
 - Growth-pupariation time
 - Locomotion-young²
 - Locomotion-old²
 - Locomotion-pupation h.²
 - Lifespan⁵
- Parkinson model
 - ▼ Development-hatching
 - ▼ Development-pupation
 - ▼ Development-eclosion
 - ▼ Locomotion
 - ▼ Lifespan

References

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Summary : Biological Effects of Low-dose Radiation

▷ Natural defenses mechanism after exposure to low-dose radiation

- Adaptive or defense responses (such as DNA damage repair, antioxidative function, and immune activation)
- Depends on the type of radiation, doses and dose rates, cell- or tissue-type etc.
- These protective systems play an important role in the final biological phenotype after LDR exposures.

▷ Dose-response model based on radiobiological evidence reviewed

- The LNT model dose not fully account for biological effects of low dose (and low dose rate) radiation.
- The possibility of existence of other dose-response models such as threshold or hormetic model cannot be ruled out.
- More research is needed to appropriately determine the dose-response relationship of low dose radiation.

Our life & Radiation.....

*“All things are poison,
and nothing is without poison;
the dosages alone makes it
so a thing is not a poison.”*

– Paracelsus (1493–1541) –

Thank you for your attention~

