Low-dose radiation, diabetes & its complications

Lu Cai

Departments of Pediatrics, Radiation Oncology, and Pharmacology & Toxicology

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Dose-Response Annual Meeting
Amherst, April 21-22, 2015

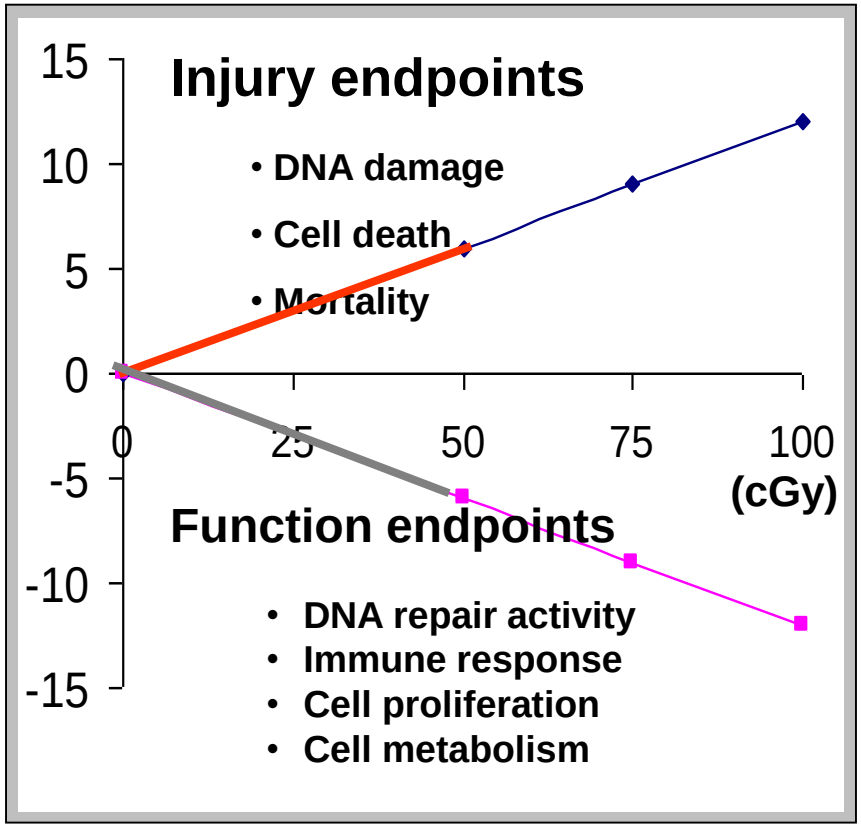
- **LDR/LDR-induced hormesis and adaptive response**
- **LDR preventive effects on various injuries**
- **Diabetes/Diabetic complications**
- **Possible mechanisms**
- **Current debates for the risks & benefits**

LDR, Diabetes & Diabetic Complications

UNSCEAR 1986 report: (United Nations Scientific Committee on the Effects of Atomic Radiation)

- Low LET radiation
  - < 20 rad (200 mGy)
- High LET radiation
  - < 5 rad (50 mGy)
- Low dose rate
  - < 0.05 mGy/min

Before

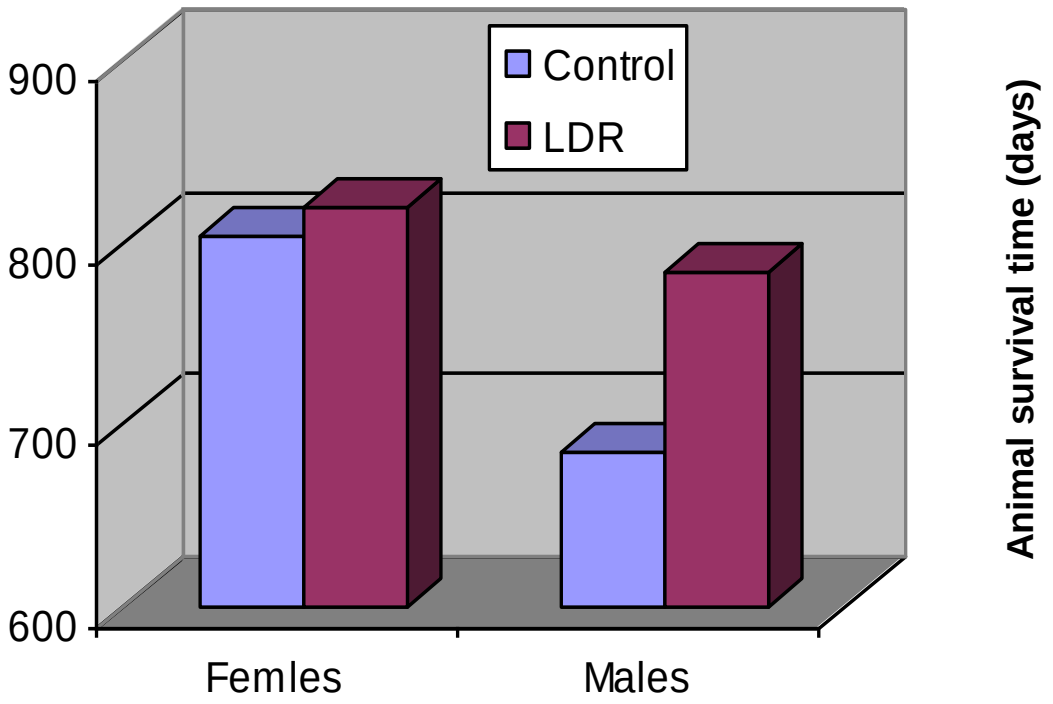

15
10
5
0
-5
-10
-15
0
25
50
75
100
(cGy)
Injury endpoints
• DNA damage
• Cell death
• Mortality
Function endpoints
• DNA repair activity
• Immune response
• Cell proliferation
• Cell metabolism

Hormesis: *Life longevity*

J Natl Cancer Inst. 1955 Feb;15(4):1049-58.

Long-term effects of acute and chronic irradiation in mice. I. Survival and tumor incidence following chronic irradiation of 0.11 r per day.

LORENZ E, HOLLCROFT JW, MILLER E, CONGDON CC, SCHWEISTHAL R.



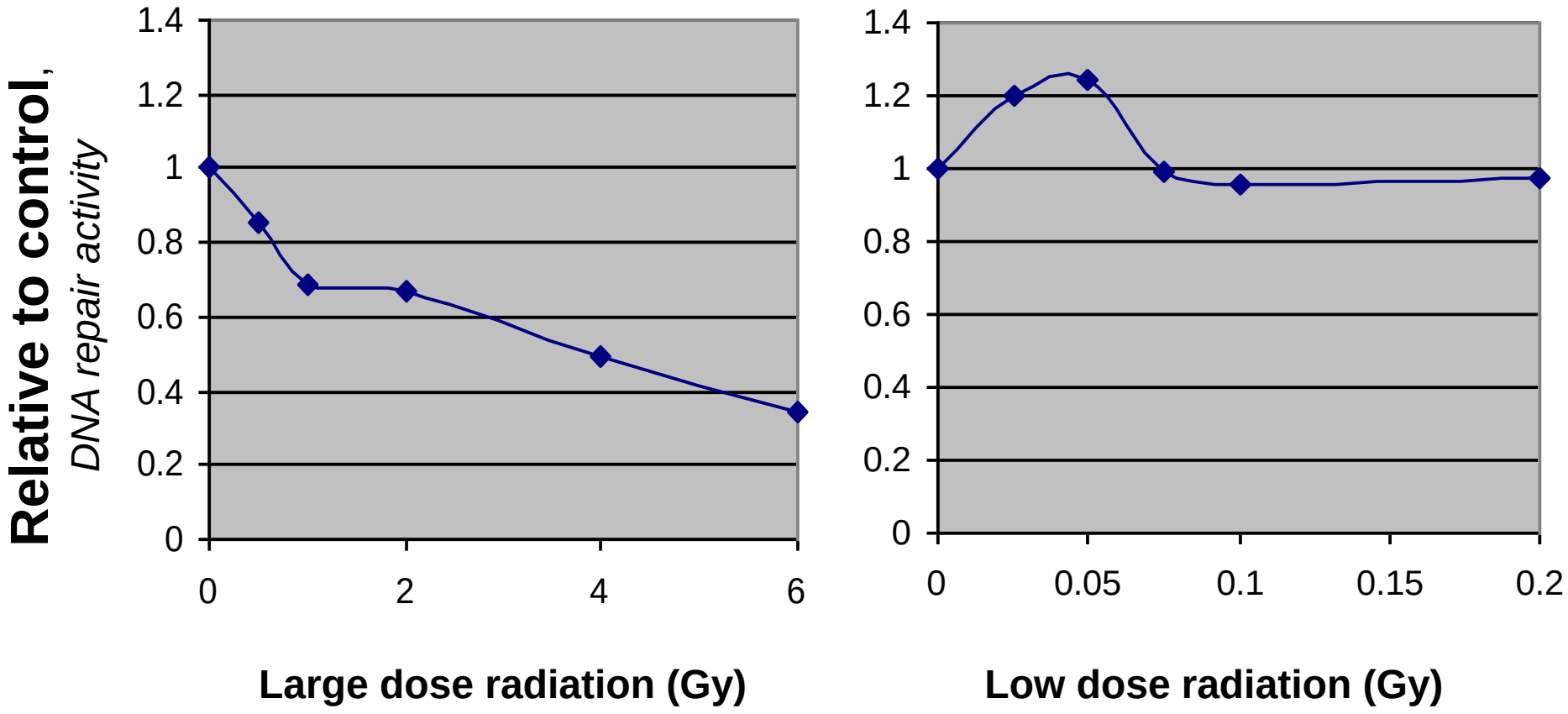
Hormesis: *DNA repair and antioxidant activities*

- Feinendegen LE, Muhlensiepen H, Bond VP, Sondhaus CA. Intracellular stimulation of biochemical control mechanisms by low-dose, low-LET irradiation. Health Phys. 1987 May;52(5):663-9.

- Liu SZ, **Cai L**, Sun JB. Effect of low-dose radiation on repair of DNA and chromosome damage. Acta Biol Hung. **1990**;41(1-3):149-57.

- Maeda T, Chua PP, Chong MT, Sim AB, Nikaido O, Tron VA. Nucleotide excision repair genes are upregulated by low-dose artificial ultraviolet B: evidence of a photoprotective SOS response? J Invest Dermatol. 2001 Dec;117(6):1490-7.

Hormesis: *DNA repair and antioxidant activities*

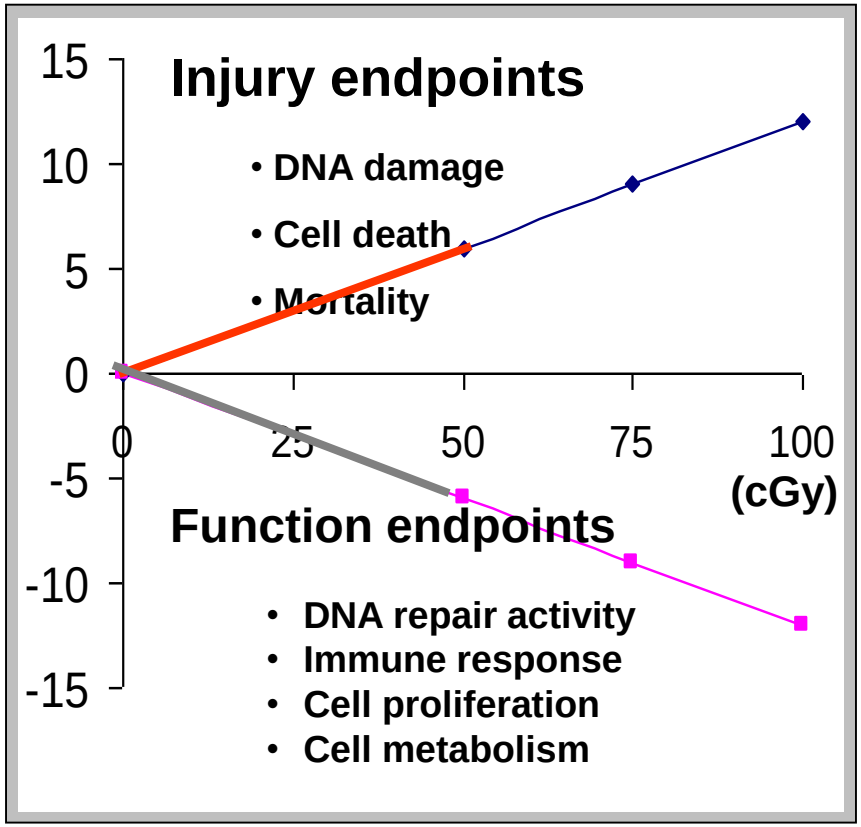


Liu SZ et al. 1990

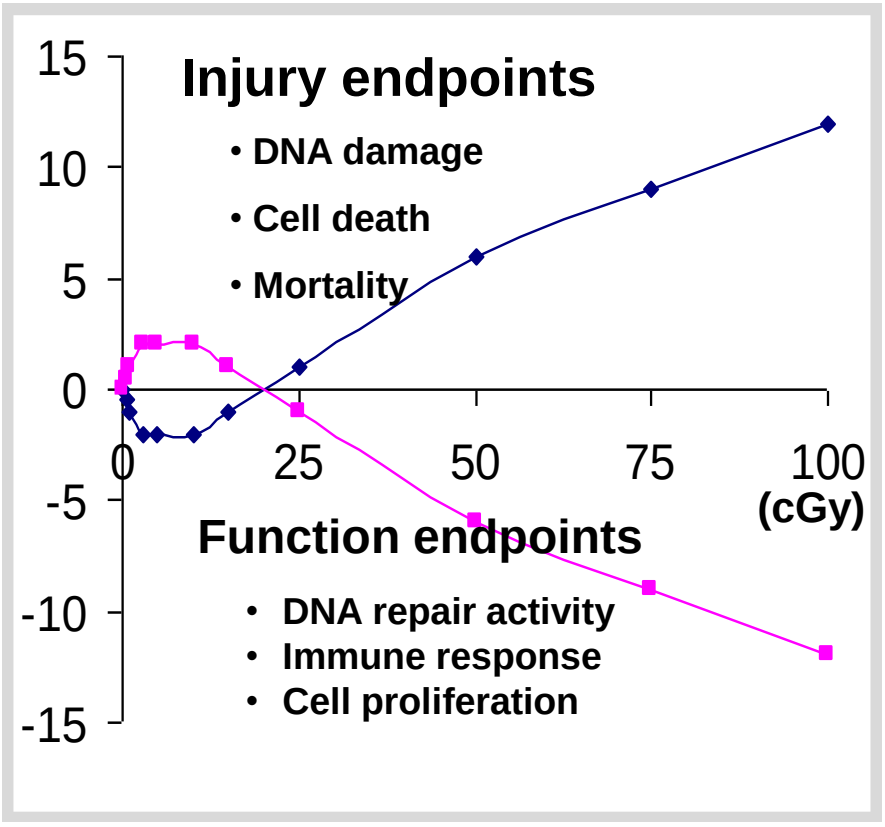
Hormesis: *DNA repair and antioxidant activities*

- Kojima S, et al. Localization of **glutathione and induction of glutathione synthesis-related** proteins in mouse brain by low doses of gamma-rays. Brain Res. 1998 Oct 19;808(2):262-9.
- Kojima S, et al. Induction of mRNAs for **glutathione synthesis-related proteins** in mouse liver by low doses of gamma-rays. Biochim Biophys Acta. 1998 Aug 24;1381(3):312-8.
- Kojima S, et al. Elevation of **antioxidant potency** in the brain of mice by low-dose gamma-ray irradiation and its effect on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced brain damage. Free Radic Biol Med. 1999 Feb;26(3-4):388-95.
- Yamaoka K, et al. Changes of **SOD-like substances** in mouse organs after low-dose X-ray irradiation. Physiol Chem Phys Med NMR. 1999;31(1):23-8.
- Kojima S, et al. **Possible role of elevation of glutathione** in the acquisition of enhanced proliferation of mouse splenocytes exposed to small-dose gamma-rays. Int J Radiat Biol. 2000 Dec;76(12):1641-7.

Before



Now



Hormesis
(U-shape curve)
(suppression & stimulation)

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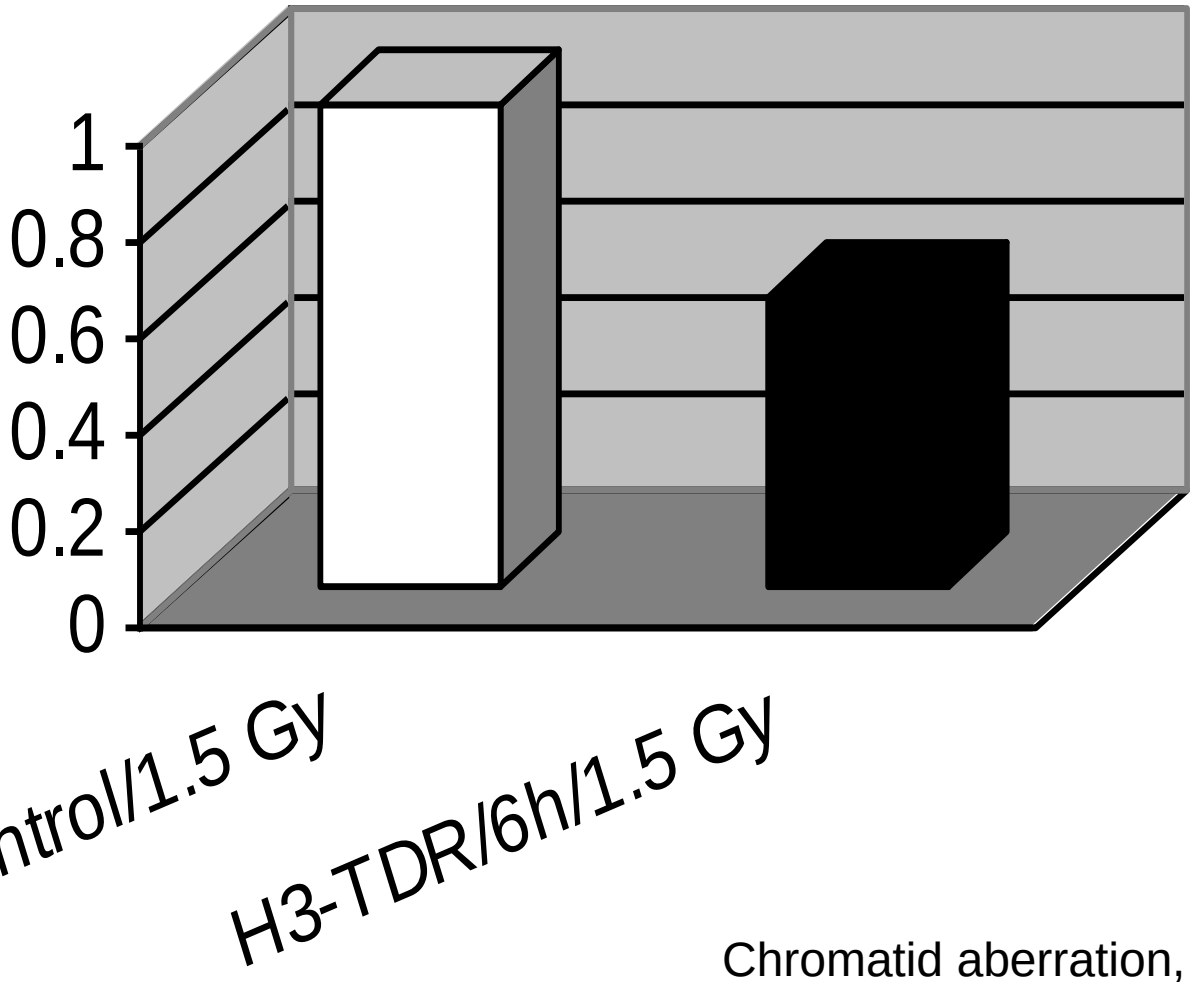
Adaptive response

Science 1984, 223(4636):594-7.

Adaptive response of human lymphocytes to low concentrations of radioactive thymidine.

Olivieri G, Bodycote J, Wolff S.



Chromatid aberration,

cytogenetic adaptive response

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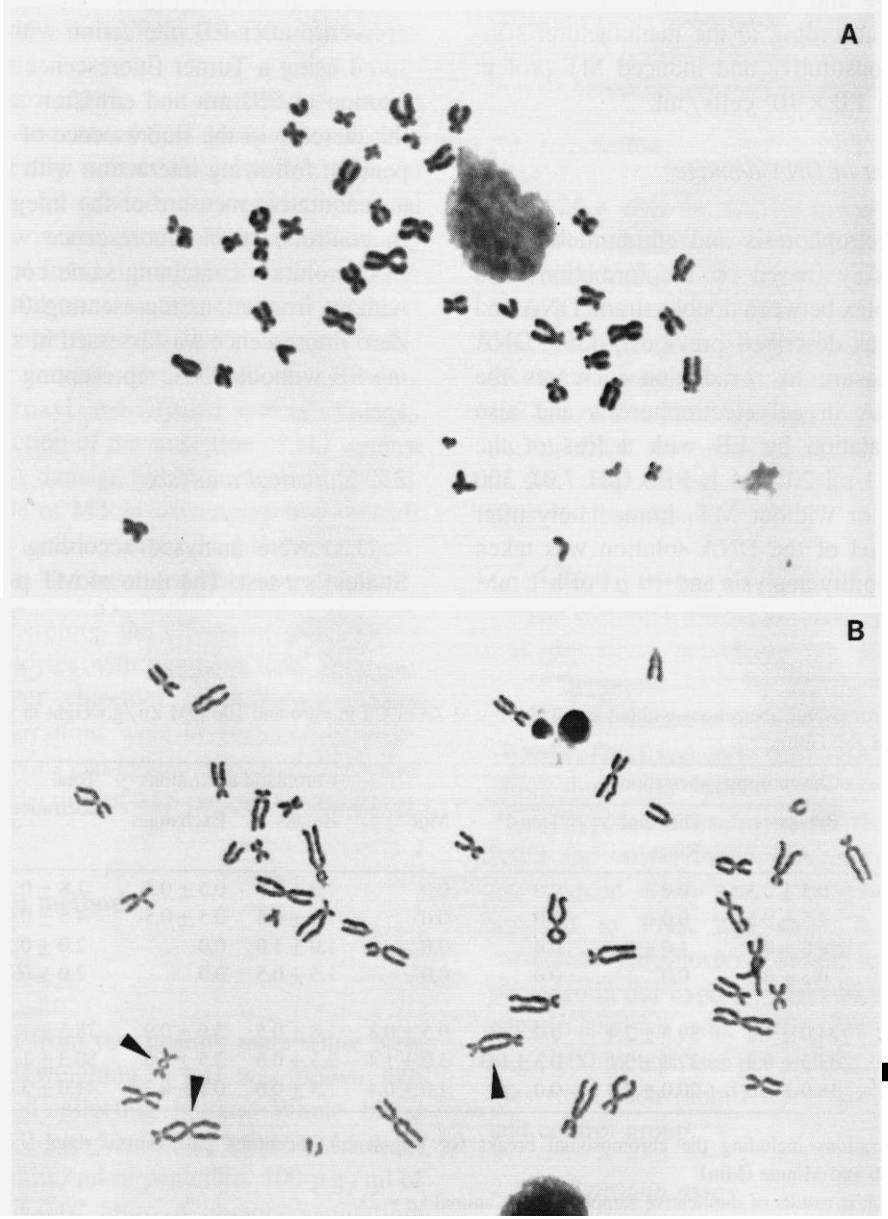
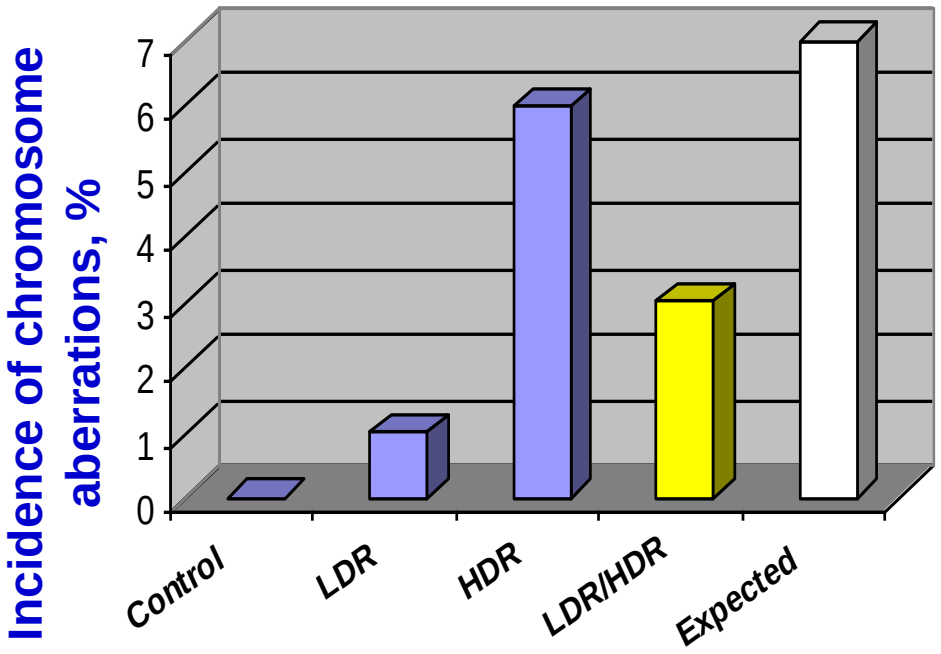
Adaptive response





Cai L and Liu 1990

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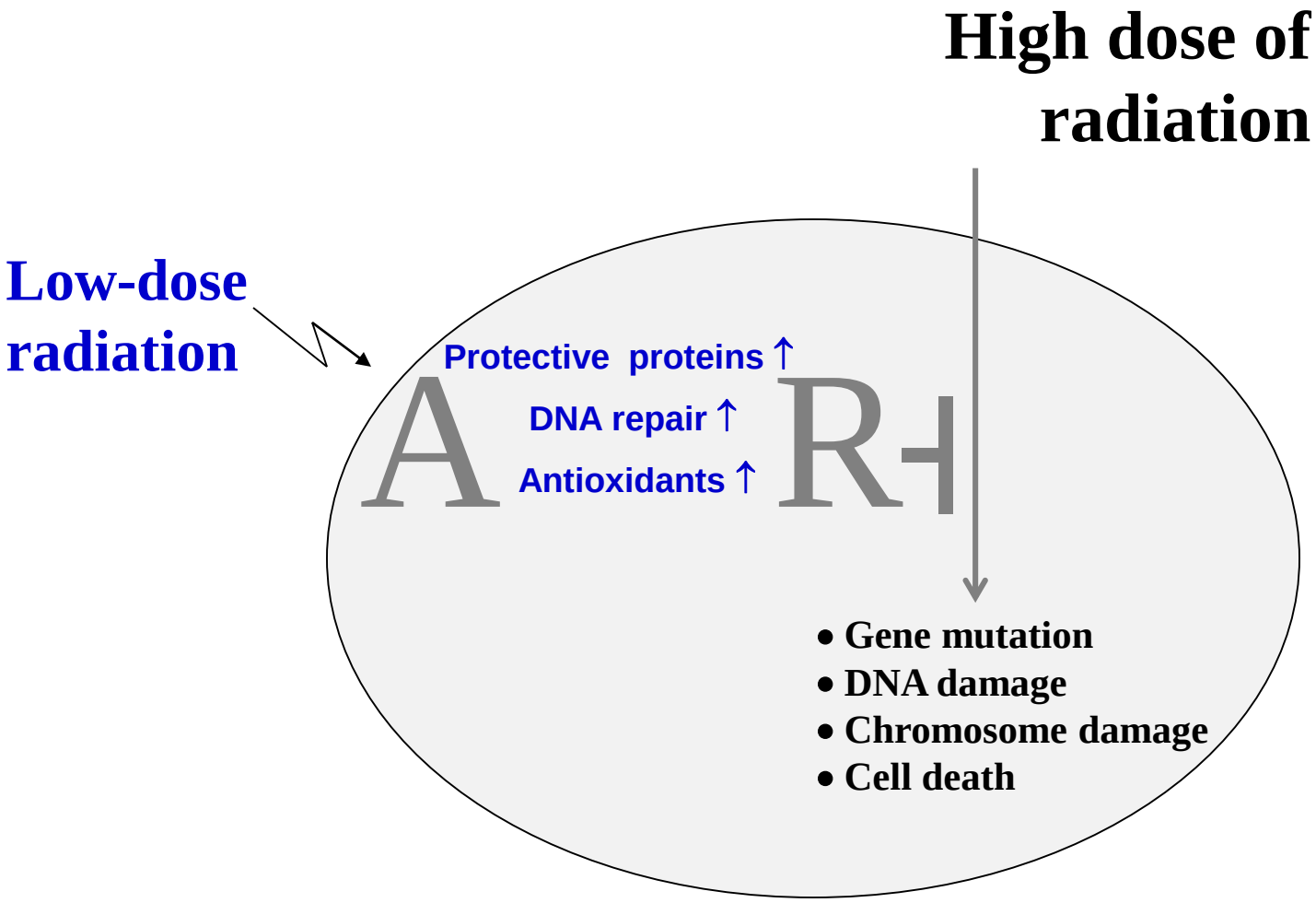
Adaptive response



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Adaptive response

- **Cai L**, Liu SZ. Induction of cytogenetic adaptive response of somatic and germ cells in vivo and in vitro by low-dose X-irradiation. Int J Radiat Biol. **1990** Jul;58(1):187-94.
- **Cai L**, Jiang J, Wang B, Yao H, Wang X. Induction of an adaptive response to dominant lethality and to chromosome damage of mouse germ cells by low dose radiation. Mutat Res. 1993 Dec;303(4):157-61.
- **Cai L**, Wang P. Induction of a cytogenetic adaptive response in germ cells of irradiated mice with very low-dose rate of chronic gamma-irradiation and its biological influence on radiation-induced DNA or chromosomal damage and cell killing in their male offspring. Mutagenesis. 1995 Mar;10(2):95-100.
- **Cai L**, Cherian MG. Adaptive response to ionizing radiation-induced chromosome aberrations in rabbit lymphocytes: effect of pre-exposure to zinc, and copper salts. Mutat Res. 1996 Aug 12;369(3-4):233-41.
- **Cai L**. Research of the adaptive response induced by low-dose radiation: where have we been and where should we go? Hum Exp Toxicol. 1999 Jul;18(7):419-25.
- Wang GJ, **Cai L**. Induction of cell-proliferation hormesis and cell-survival adaptive response in mouse hematopoietic cells by whole-body low-dose radiation. Toxicol Sci. 2000 Feb;53(2):369-76.

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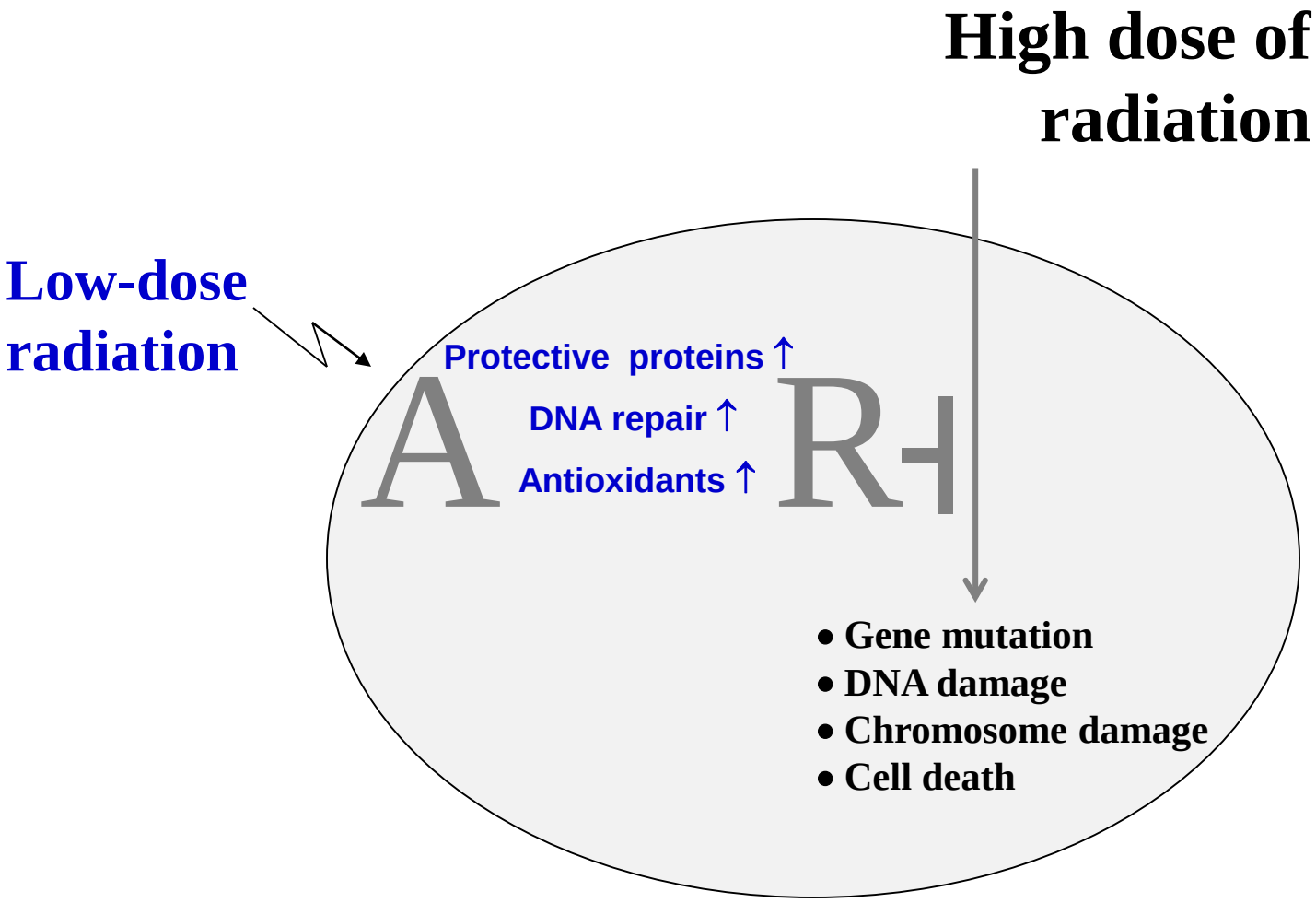
Adaptive response



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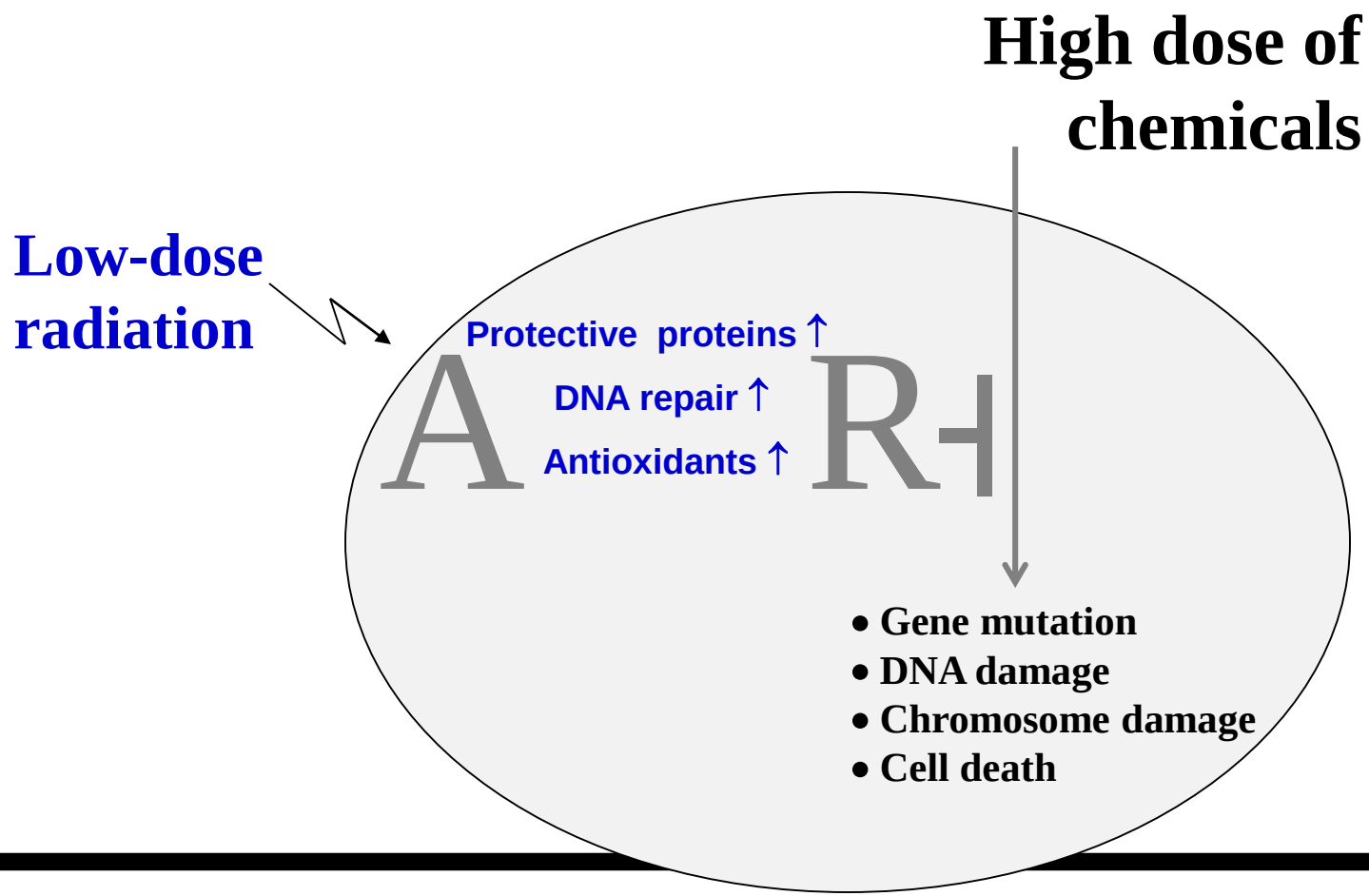
Adaptive response

(Cross adaptive response)



Human & Experimental Toxicology (1999) 18, 419–425

http://www.stockton-press.co.uk/het

1999

Research of the adaptive response induced by low-dose radiation: where have we been and where should we go?

L Cai*,[1,2]

[1]Department of Pathology, The University of Western Ontario, London, Ontario N61 5C1, Canada; [2]Institute of Radiation Medicine, Norman Bethune University of Medical Sciences, Changchun 130021, People's Republic of China

Can we use the hormesis and/or adaptive response induced by LDR to clinic setting?

inducing AR are called adapting dose of AR dose. So far, AR has been characterized both *in vitro* with human, rabbit and calf lymphocytes, normal or tumor cell lines, and *in vivo* with mouse bone marrow cells, splenocytes and germ cells.[2,3] AR could be expressed in multiple biological endpoints including unscheduled DNA synthesis, micronuclei, chromosome aberrations, gene muta-

like to discuss the following questions:

How does the AR dose relate to human environmental (ecological) exposure?

Humans live with a background radiation which may play an essential role in human health

- **LDR/LDR-induced hormesis and adaptive response**
- **LDR preventive effects on various injuries**
- **Diabetes/Diabetic complications**
- **Possible mechanisms**
- **Current debates for the risks & benefits**

J. Radiat. Res., 45, 89–95 (2004)

Regular Paper

Inhibitory Effects of Prior Low-dose X-ray Irradiation on Carbon Tetrachloride-induced Hepatopathy in Acatalasemic Mice

Kiyonori YAMAOKA[1]*, Takahiro KATAOKA[1], Takaharu NOMURA[2], Takehito TAGUCHI[1],

SETAC PRESS Environmental Toxicology and Chemistry, Vol. 30, No. 3, pp. 640–649, 2011

Printed in the USA
DOI: 10.1002/etc.423

THE EFFECTS OF ENVIRONMENTAL LOW-DOSE IRRADIATION ON TOLERANCE TO CHEMOTHERAPEUTIC AGENTS

Eric K. Howell,† Sergey P. Gaschak,‡ Kenneth D. W. Griffith,† and Brenda E. Rodgers*†
†Department of Biological Sciences and the Center for Environmental Radiation Studies, Texas Tech University, Lubbock, Texas, USA
‡International Radioecology Laboratory, Slavutych, Ukraine

(*Submitted* 12 *July* 2010; *Returned for Revision* 30 *August* 2010; *Accepted* 22 *September* 2010)

Abstract—The nuclear disaster at Chernobyl, Ukraine, in April of 1986 continues to impact the environment on many different levels. Studies of epidemiological, environmental, and genetic impacts have been prolific since the accident, revealing interesting results concerning the effects of radiation. The long-tailed field mouse, *Apodemus flavicollis*, was collected from distinct localities near the Chernobyl site and evaluated based on in vivo responses to the current clinically employed chemotherapeutic agents bleomycin (BLM) and vinblastine (VBL), as well as the immune modulator lipopolysaccharide (LPS). Maximum tolerable doses of three different cancer drugs were administered to the rodents from three different lifestyles: native mice living and reproducing in a radioactive environment,

J. Radiat. Res., 48, 505–513 (2007)

Regular Paper

Inhibitory Effects of Prior Low-dose X-irradiation on Ischemia-reperfusion Injury in Mouse Paw

Takahiro KATAOKA, Yuko MIZUGUCHI, Masaaki YOSHIMOTO, Takehito TAGUCHI and Kiyonori YAMAOKA*

Edema/Ischemia-reperfusion injury/Low-dose irradiation/Reactive oxygen species/Antioxidation function.

We have reported that low-dose, unlike high-dose, irradiation enhanced antioxidation function and reduced oxidative damage. On the other hand, ischemia-reperfusion injury is induced by reactive oxygen species. In this study, we examined the inhibitory effects of prior low-dose X-irradiation on ischemia-reperfusion injury in mouse paw. BALB/c mice were irradiated by sham or 0.5 Gy of X-ray. At 4 hrs after irradiation, the left hind leg was bound 10 times with a rubber ring for 0.5, 1, or 2 hrs and the paw thickness was measured. Results show that the paw swelling thickness by ischemia for 0.5 hr was lower than that for 2 hrs. At 1 hr after reperfusion from ischemia for 1 hr, superoxide dismutase activity in serum was increased in those mice which received 0.5 Gy irradiation and in the case of the ischemia for 0.5 or 1 hr, the paw swelling thicknesses were inhibited by 0.5 Gy irradiation. In addition, interstitial edema in those mice which received 0.5 Gy irradiation was less than that in the mice which underwent by sham irradiation. These findings suggest that the ischemia-reperfusion injury is inhibited by the enhancement of antioxidation function by 0.5 Gy irradiation.

Inflammation, Vol. 35, No. 1, February 2012 (© 2011)
DOI: 10.1007/s10753-011-9293-9

Inhibitory Effects of Prior Low-dose X-irradiation on Cold-induced Brain Injury in Mouse

Masaaki Yoshimoto,[1] Takahiro Kataoka,[1] Teruaki Toyota,[1] Takehito Taguchi,[1] and Kiyonori Yamaoka[1,2]

Abstract—We examined the inhibitory effects of low-dose X-irradiation on mouse brain tissue with cold-induced injury by comparing tissue samples from three groups of mice: control, sham-irradiated cold-exposed, and X-ray-irradiated (0.5 Gy) cold-exposed mice. The water content in brain increased significantly in the sham-irradiated group following the cold-induced injury relative to the control group. However, water content in brain tissue from the X-ray-irradiated group was significantly lower than that from the sham-irradiated group. Levels of antioxidants, such as superoxide dismutase and glutathione, in brain tissue from the X-ray-irradiated group were higher than those from the sham-irradiated group. Moreover, the cold injury-induced cell death, particularly apoptosis, while low-dose irradiation inhibited cell death, especially among glial cells, but not numeral cells. These findings suggest that prior low-dose X-irradiation activated antioxidant function and inhibited cold-induced brain injury.

KEY WORDS: cold injury; brain edema; 0.5 Gy irradiation; antioxidative function.

Human & Experimental Toxicology (2008) 27: 135–142

Human & Experimental Toxicology 2008

BELLE Article:

Low-dose radiation and its clinical implications: diabetes

Guan-Jun Wang[1], Xiao-Kun Li[2], Kazuo Sakai[3] and Lu Cai[1,2,4*]

[1]Department of Hematology and Oncology, The First University Hospital, Jilin University Medical College, Changchun 130021, People's Republic of China;
[2]Department of Biopharmacy, College of Pharmacy, and Biopharmaceutical Research & Development Center, Jinan University, Guangzhou 510080, People's Republic of China;
[3]Low Dose Radiation Research Center, Central Research Institute of Electric Power Industry, 2-11-1 Iwado-Kita, Kome 201-8511, Tokyo;
[4]Departments of Medicine, Pharmacology and Toxicology, and Radiation Oncology, University of Louisville School of Medicine, Louisville, KY 40202, USA

Induction of hormesis and adaptive response by low-dose radiation (LDR) has been extensively indicated. Adaptive response induced by LDR was not only resistant to damage caused by a subsequently high-dose radiation, but also cross-resistant to other non-radiation challenges, such as chemicals. Mechanisms by which LDR induces the preventive effect on radiation- or chemical-induced tissue damage include induced or up-regulated expression of protective proteins, such as heat shock proteins and antioxidants. Since oxidative damage to tissues is a low-intensity or power laser (LIL or LPL) radiation on skin wound healing, which has stimulated clinical use of LIL to cure skin ulcer in diabetic patients. Mechanisms by which LDR prevents diabetes, though are unclear now, may include the induction of pancreatic antioxidants to prevent β cell from oxidative damage and immunomodulation to preserve pancreatic function. For LIL therapeutic effect on diabetic wound healing, mechanisms may include its antioxidant action, immunomodulation, cell proliferation stimulation as well as improvement of sys-

- **LDR/LDR-induced hormesis and adaptive response**
- **LDR preventive effects on various injuries**
- **Diabetes/Diabetic complications**
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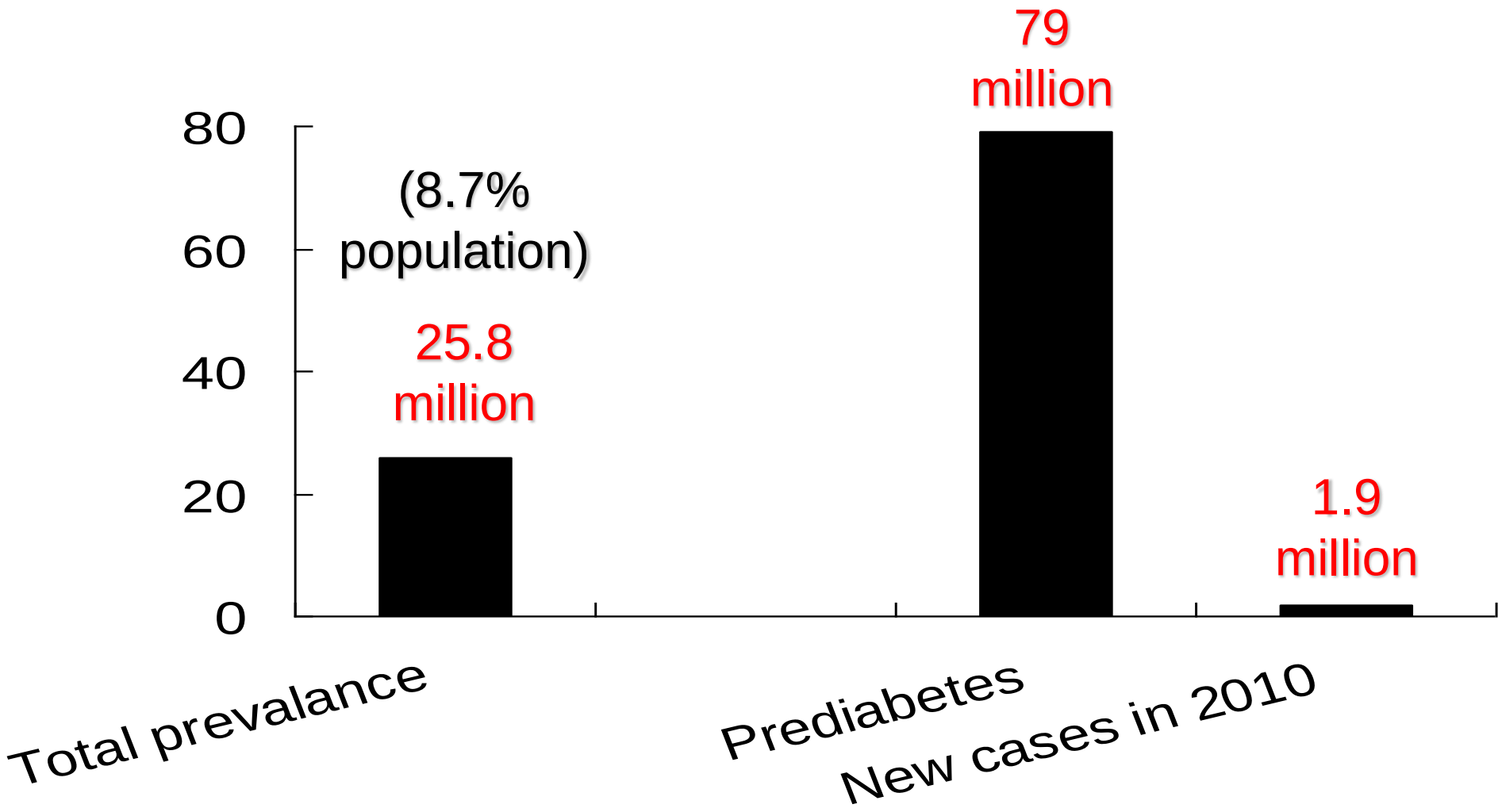
National Diabetes Fact Sheet, 2011



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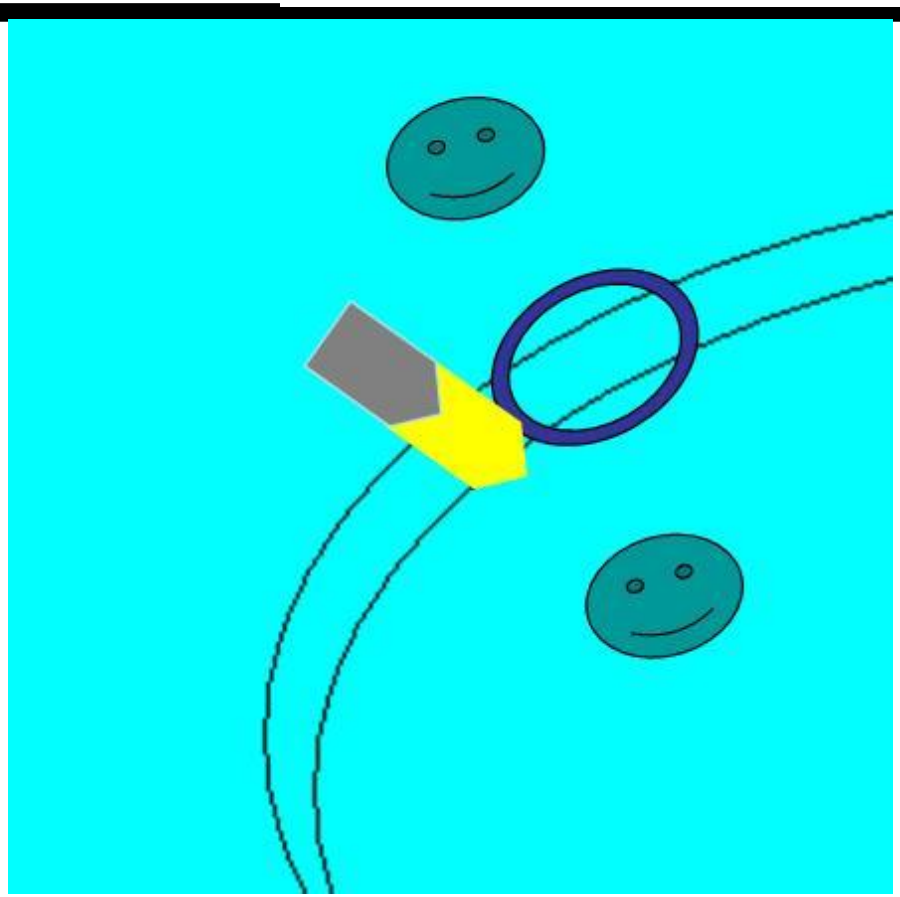
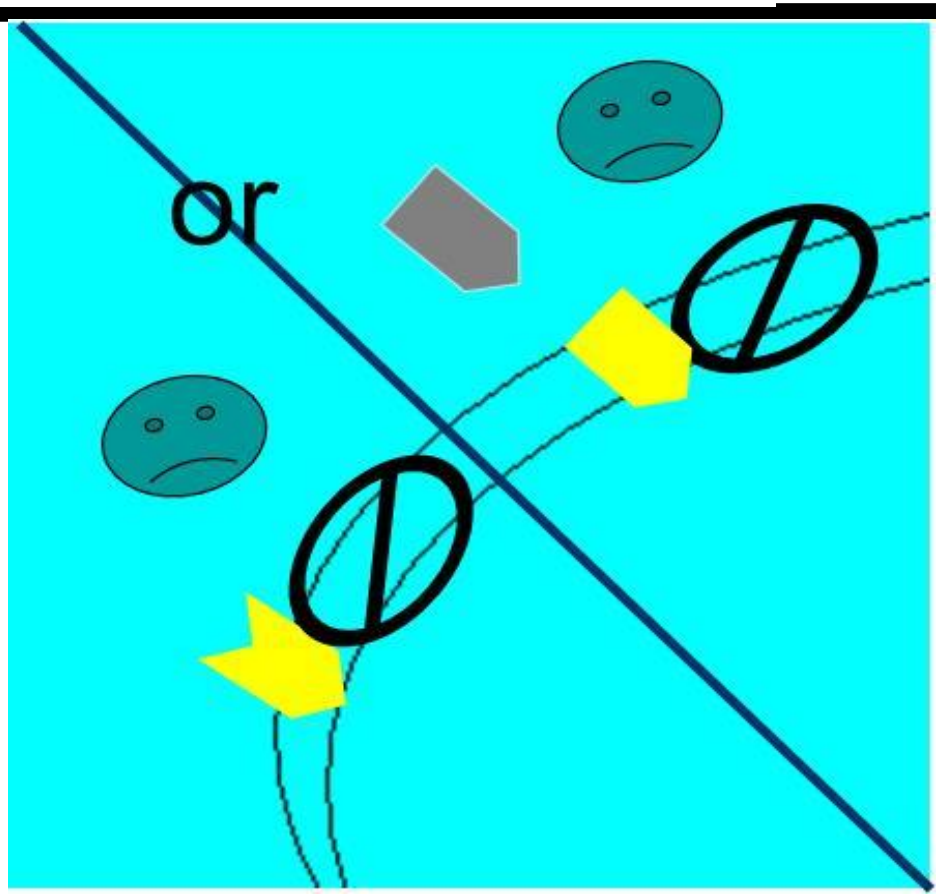
Normal



Diabetes



Diabetes is a metabolic disorder that is characterized by high blood glucose and either insufficient or ineffective insulin.

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Hyperglycemia, hyperlipidemia, hypertension & inflammation

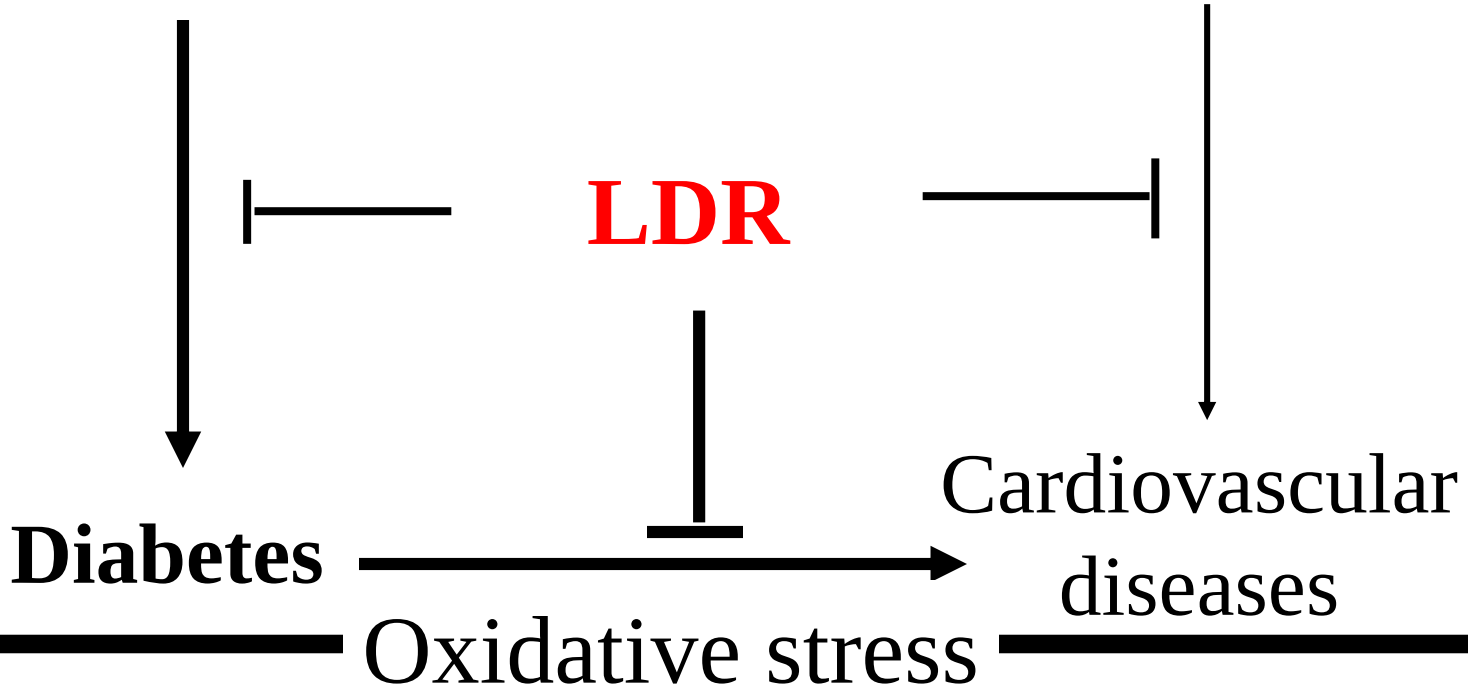
Oxidative stress

Diabetes → Cardiovascular diseases

Oxidative stress

Hyperglycemia, hyperlipidemia, hypertension & inflammation

Oxidative stress



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Physiol Chem Phys Med NMR. **1995**;27(3):149-59.

Protection against alloxan diabetes by low-dose 60Co gamma irradiation before alloxan administration.

Takehara Y, Yamaoka K, Hiraki Y, Yoshioka T, Utsumi K.

LDR:

- **Increases pancreatic SOD,**
- **Decreases alloxan-induced pancreatic oxidative damage**
- **No hyperglycemia**

RADIATION RESEARCH **154**, 680–685 (2000)
0033-7587/00 $5.00

Prevention of Type I Diabetes by Low-Dose Gamma Irradiation in NOD Mice

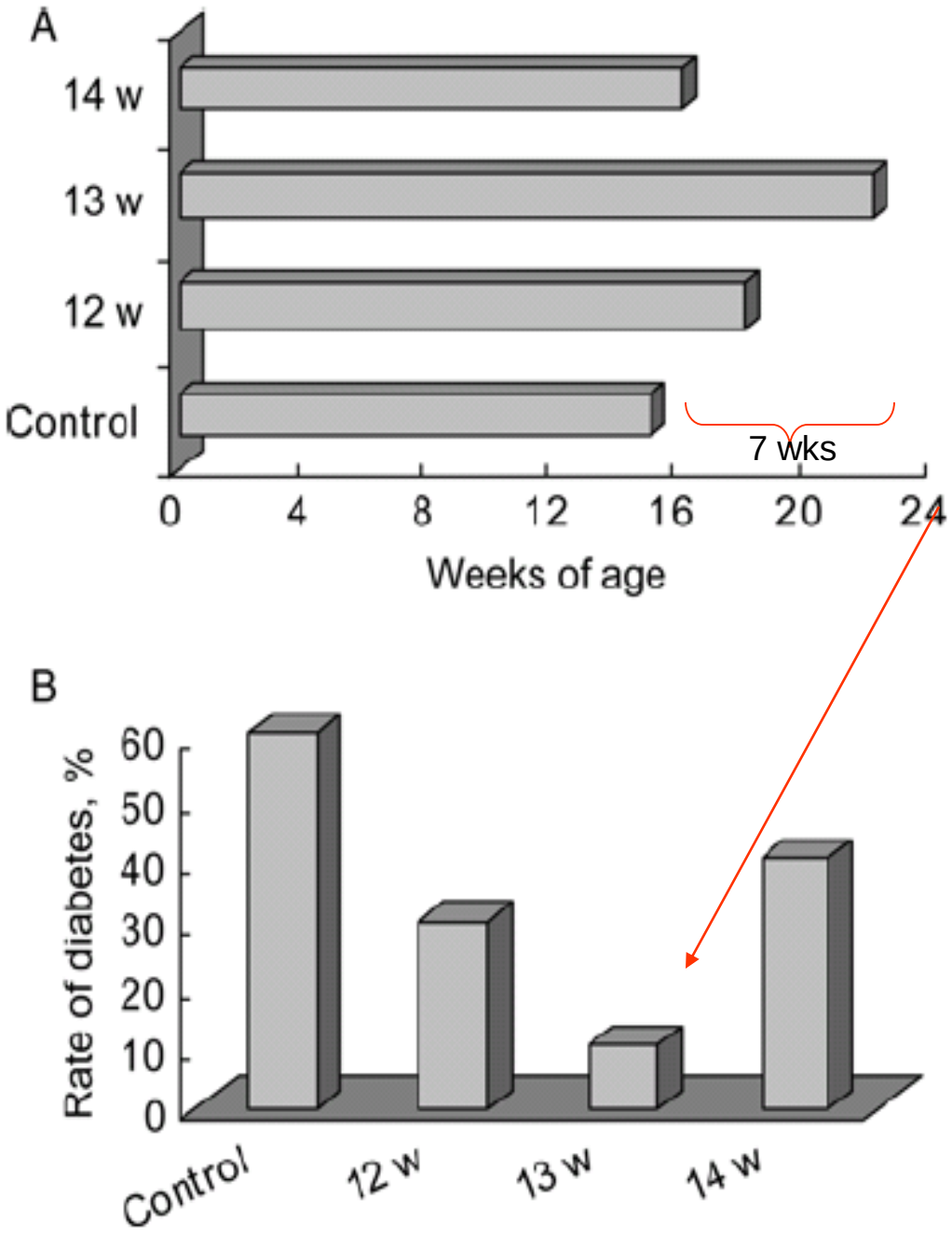
Mareyuki Takahashi,[a,1] Shuji Kojima,[b] Kiyonori Yamaoka[c] and Etsuo Niki[a]

[a] *Research Center for Advanced Science and Technology, University of Tokyo, 4-6-1 Komaba, Meguro, Tokyo 153-8904, Japan;* [b] *Research Institute for Biosciences, Science University of Tokyo, 2669 Yamazaki, Noda, Chiba 278-0022, Japan; and* [c] *Bioscience Department, Central Research Institute of Electric Power Industry, 2-11-1 Iwado Kita, Komae, Tokyo 201-0004, Japan*

Takahashi, M., Kojima, S., Yamaoka, K. and Niki, E. Prevention of Type I Diabetes by Low-Dose Gamma Irradiation in NOD Mice. ***Radiat. Res.*** **154, 680–685 (2000).**

Pretreatment with nonlethal, low-dose irradiation has been shown to have a protective effect against oxidative injury in animal tissues. Since oxidative injury of tissues is known to be a major cause of many human diseases, we examined the effect of low-dose irradiation on the progression of type I diabetes in mice. Nonobese diabetic (NOD) mice were treated with γ irradiation and the progression of the disease was monitored. An elevated level of glucose in urine was first detected at 15 weeks of age in the control NOD mice, whereas the detection was delayed as long as 7 weeks when the mice received a single dose of 0.5 Gy total-body irradiation between 12 and 14 weeks of age. The greatest effect was observed in

in insects (*1*), increased resistance to oxygen toxicity (*2*), improvement of social behavior in mice (*3*), and enhancement of immune function (*4*). In an attempt to assess the biological implications of low-dose irradiation, levels of antioxidant enzymes have been studied. Manno *et al.* first reported an enhancement of SOD activity in rat liver by low-dose irradiation (*5*). Increased activities of SOD (*6–10*), glutathione peroxidase (GPx) (*7, 10*), and catalase (*10*) induced by low-dose irradiation have also been confirmed. These results have suggested the existence of significant biological effects of low-dose irradiation. Although how much such an enhancement of antioxidant enzyme activities contributes to the biological effects of radiation is not known, antioxidant defense is likely to be enhanced in the irradiated tissues.



LDR prevention of the development of diabetes in NOD mice.

Pane A represents the time point at which the first mouse from the groups with single LDR (0.5 Gy) at 12, 13 or 14 wks of age and without LDR (control group) spontaneously developed diabetes (hyperglycemia).

Results indicate that the first mouse developed diabetes is at 22 wks of age in the group of mice with LDR at 13 wks of age, which is 7 weeks later than that (15 wks of age) in control group.

Panel B represents the incidence of diabetic mice in different groups.

Results indicate that 10 % of mice with LDR at 13 wks of age developed diabetes at **24 wks of age**, which is much lower than those in control and other LDR-treated groups.

Takahashi *et al.* (2000).

RADIATION RESEARCH 167, 592–599 (2007)
0033-7587/07 $15.00

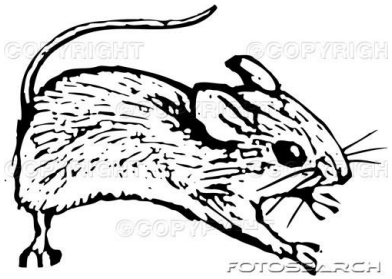
Amelioration of Type II Diabetes in *db/db* Mice by Continuous Low-Dose-Rate γ Irradiation

Mie Tsuruga,[a] Keiko Taki,[a] Genichiro Ishii,[b] Yurie Sasaki,[a] Chiharu Furukawa,[a] Takashi Sugihara,[c] Takaharu Nomura,[d] Atsushi Ochiai[b] and Junji Magae[a,1]

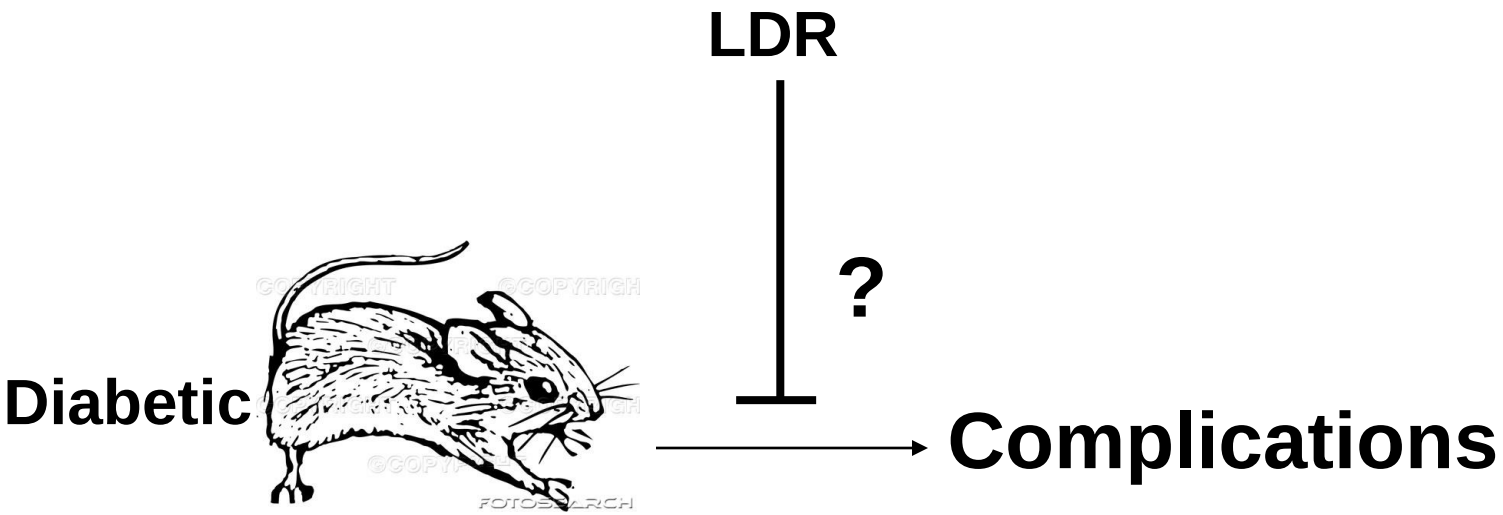
[a] *Department of Bioengineering, Institute of Research and Innovation, 1201 Takada, Kashiwa, Chiba 227-0861, Japan;* [b] *Pathology Division, Center for Innovative Oncology, National Cancer Center-Kashiwa, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan;* [c] *Department of Radiobiology, Institute for Environmental Sciences, 1-7 Ienomae, Obuchi, Rokkasho-mura, Kamikita-gun, Aomori 039-3212 Japan; and* [d] *Low Dose Radiation Research Center, Central Research Institute of Electric Power Industry, 2-11-1 Iwado-kita, Komae 201-8511, Japan*

Tsuruga, M., Taki, K., Ishii, G., Sasaki, Y., Furukawa, C., Sugihara, T., Nomura, T., Ochiai, A., and Magae, J. Amelioration of Type II Diabetes in *db/db* Mice by Continuous Low-Dose-Rate γ Irradiation. *Radiat. Res.* 167, 592–599 (2007).

Although the mechanism underlying radiation hormesis is unclear, one of the candidate molecular targets is the radiation-induced biological response to oxidative stress. ERK1/2 kinase regulating growth factor-induced intracellular signaling is activated by low-dose radiation, which



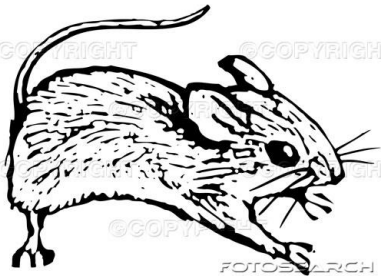
LDR ⊣ → Diabetes



Does LDR also prevent diabetic complications?

LDR

?

Diabetic 

Complications

Heart

Kidney

Skin

Neuronal system

Am J Physiol Endocrinol Metab 297: E1366–E1377, 2009.
First published September 29, 2009; doi:10.1152/ajpendo.00478.2009.

Am J Physiol Endocrinol Metab 297: E1366–E1377, 2009.
First published September 29, 2009; doi:10.1152/ajpendo.00478.2009.

Attenuation of diabetes-induced renal dysfunction by multiple exposures to low-dose radiation is associated with the suppression of systemic and renal inflammation

Chi Zhang,[1,3] Yi Tan,[2,3] Weiying Guo,[4] Cai Li,[3,5] Shunzi Ji,[1] Xiaokun Li,[1,3,6] and Lu Cai[2,3,7]

[1]School of Public Health of Jilin University, Changchun, China; [2]Department of Pediatrics, University of Louisville, Louisville, Kentucky; [3]Chinese-American Research Institute for Diabetic Complications, Wenzhou Medical College, Wenzhou; [4]The First Hospital of Jilin University; [5]School of Pharmacy of Jilin University, Changchun; [6]Engineering Research Center of Bioreactor and Pharmaceutical Development, Ministry of Education, Jilin Agricultural University, Changchun, and Key Laboratory of Biotechnology Pharmaceutical Engineering, Wenzhou Medical College, Wenzhou, China; and [7]Departments of Medicine and Radiation Oncology, University of Louisville, Louisville, Kentucky

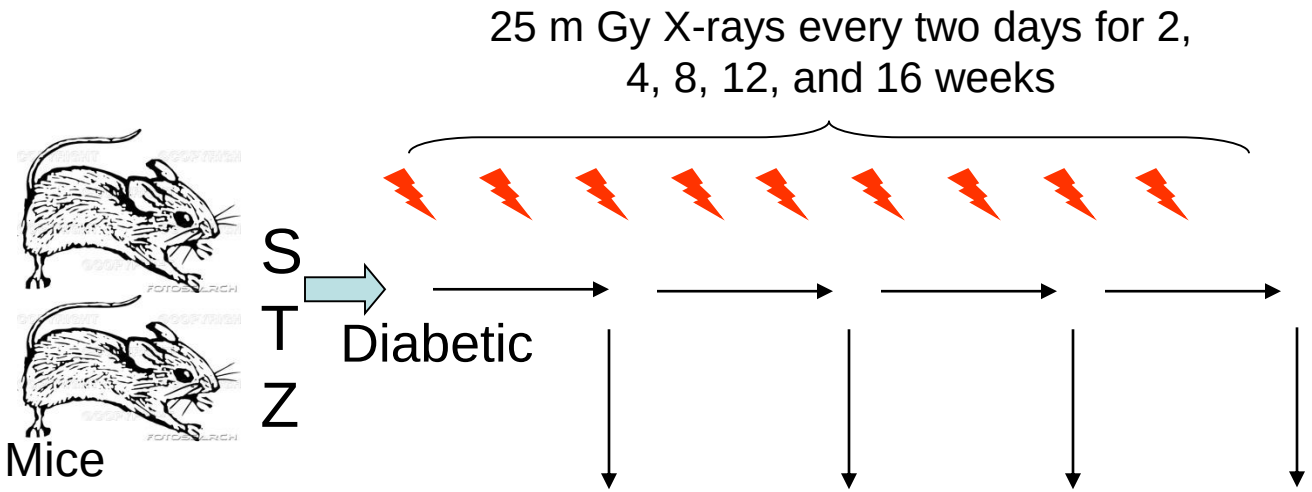
Submitted 3 August 2009; accepted in final form 27 September 2009

Zhang C, Tan Y, Guo W, Li C, Ji S, Li X, Cai L. Attenuation of diabetes-induced renal dysfunction by multiple exposures to low-dose radiation is associated with the suppression of systemic and renal inflammation. *Am J Physiol Endocrinol Metab* 297: E1366–E1377, 2009. First published September 29, 2009; doi:10.1152/ajpendo.00478.2009.—Renal protection against diabetes-induced pathogenic injuries by multiple exposures to low-dose radiation (LDR) was investigated to develop a novel approach to the prevention of renal disease for diabetic subjects. C57BL/6J mice were given multiple low-dose streptozotocin (STZ; 60 × 6 mg/kg) to produce a type 1 diabetes. Two weeks after diabetes onset, some of

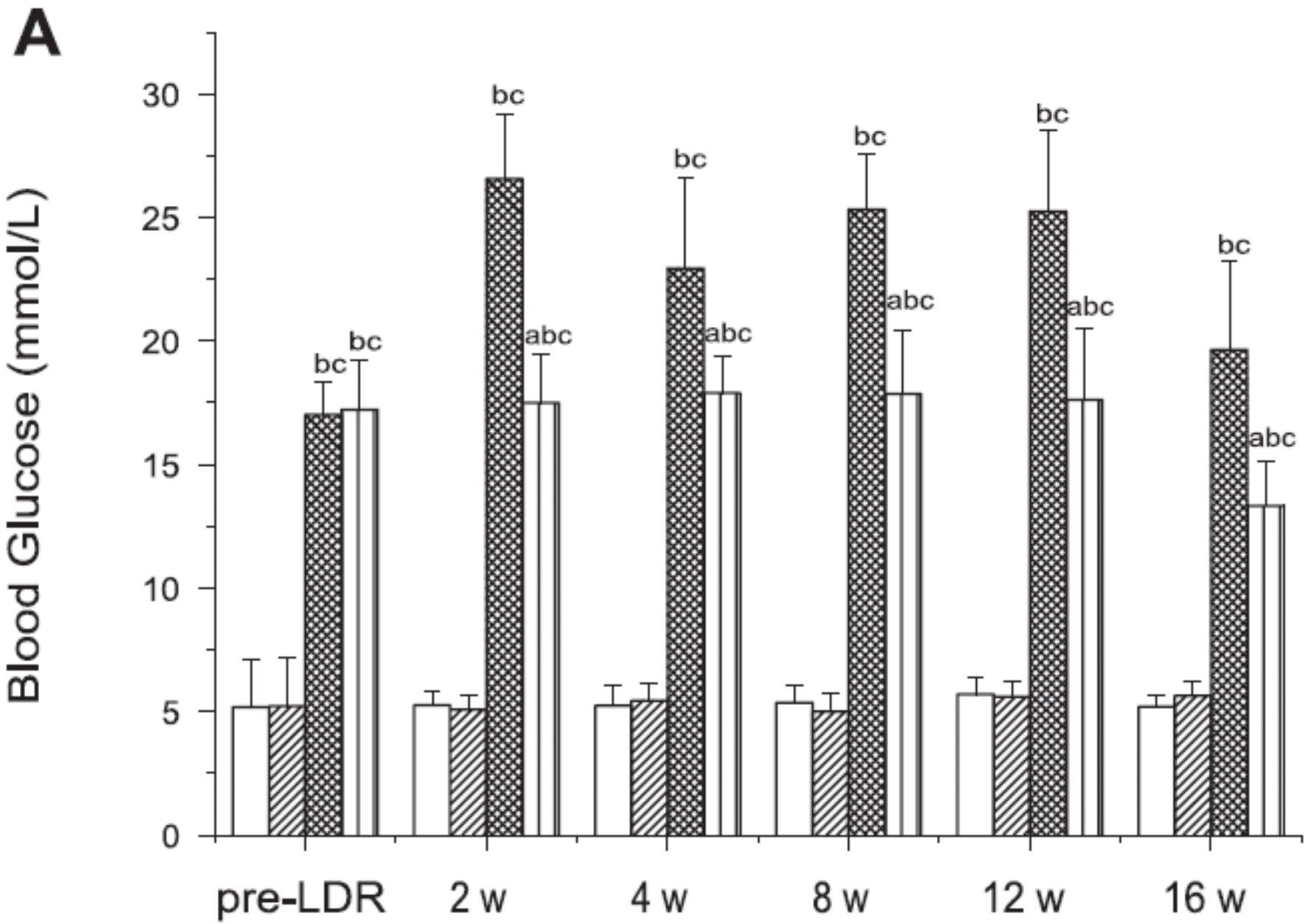
effectively preventive or therapeutic approach for DN (11). It has recently been appreciated that systemic and renal inflammation caused by hyperglycemia and hyperlipidemia play an important role in the renal oxidative damage that initiates the development of renal pathogenesis (14, 24, 26, 30).

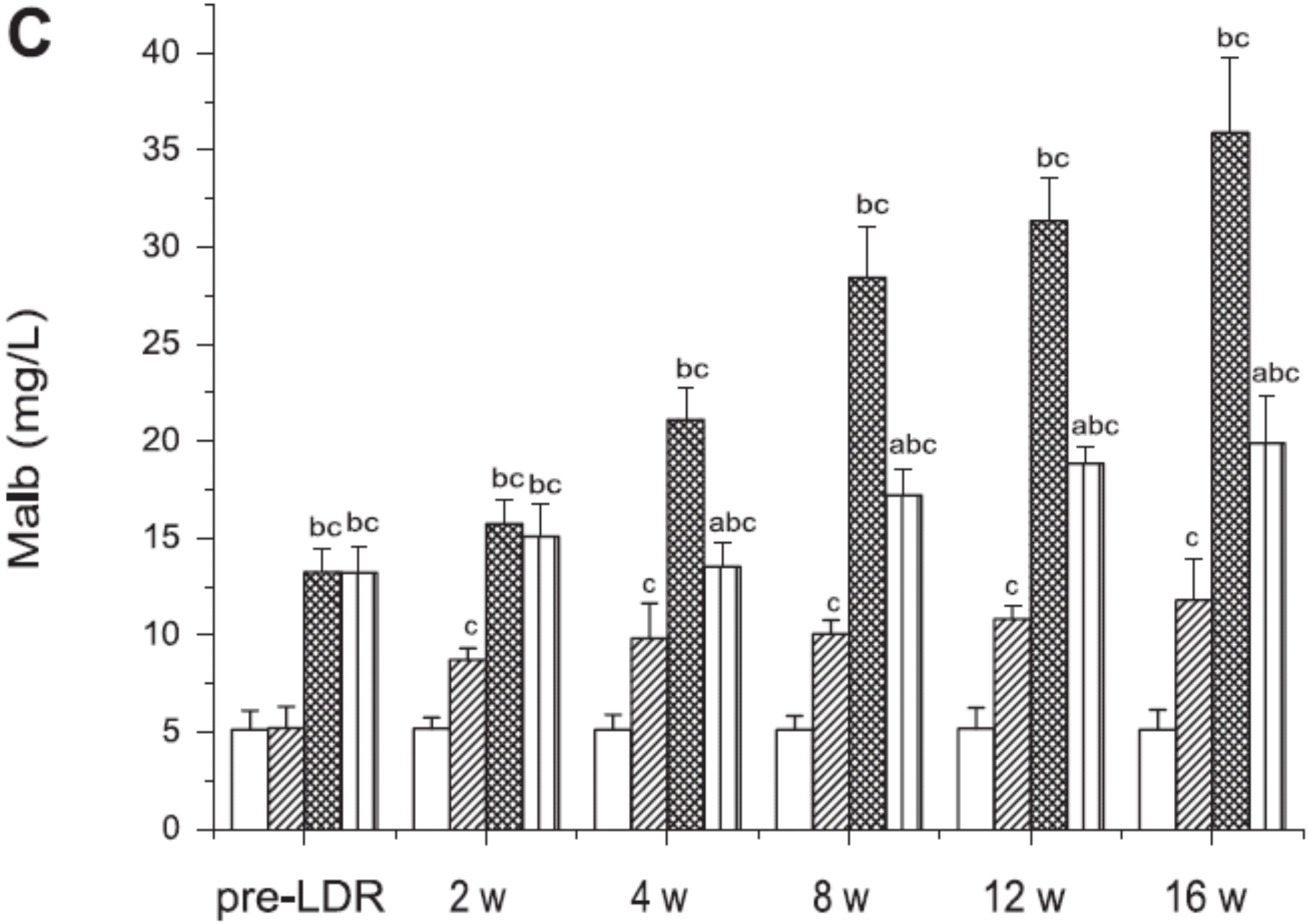
Inflammatory mediators, including adipokines, chemokines, adhesion molecules, and cytokines, were all found to play critical roles in the setting of DN (30). A growing body of evidence indicates that recruitment of inflammatory cells from

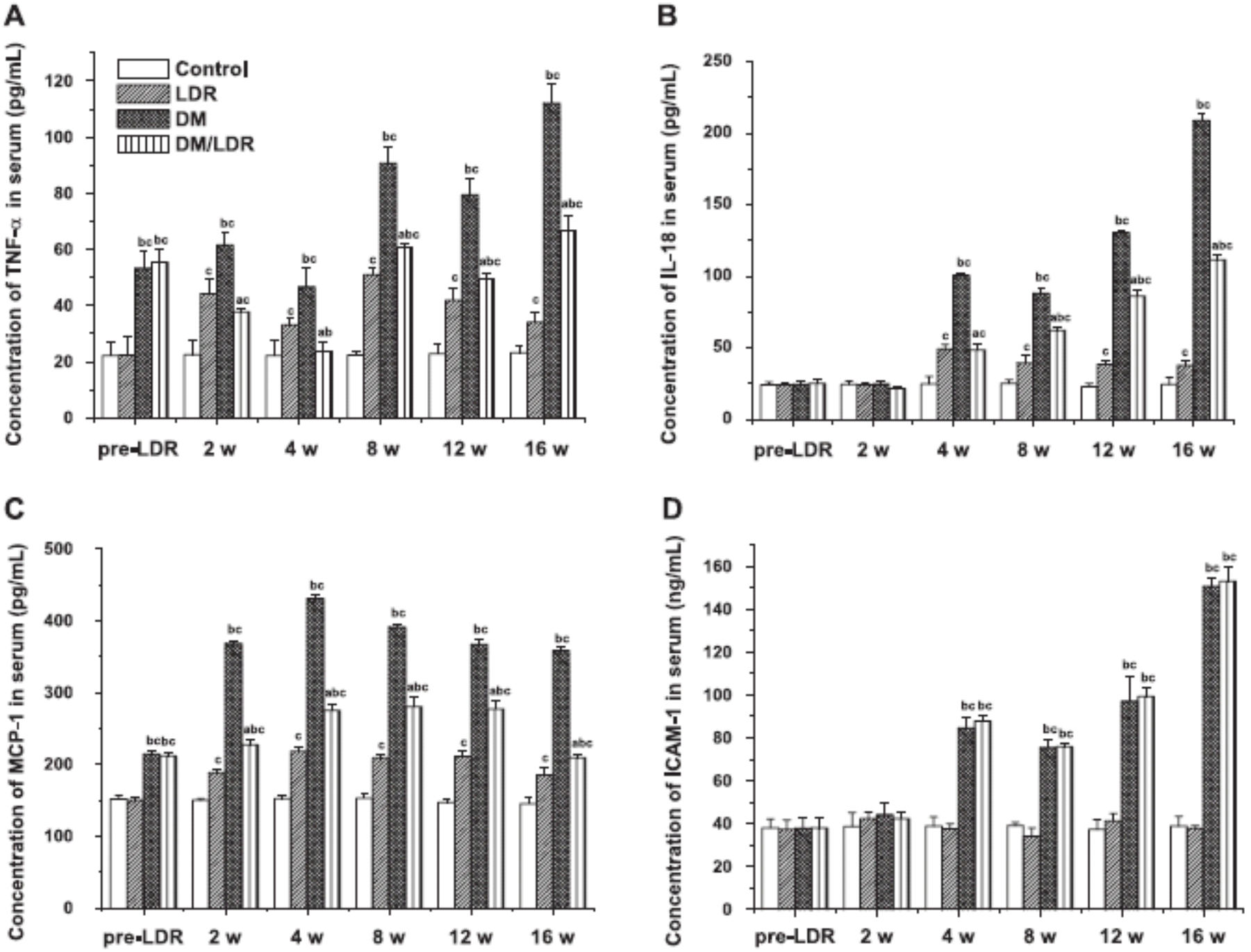
LDR's prevention of renal inflammation and damage

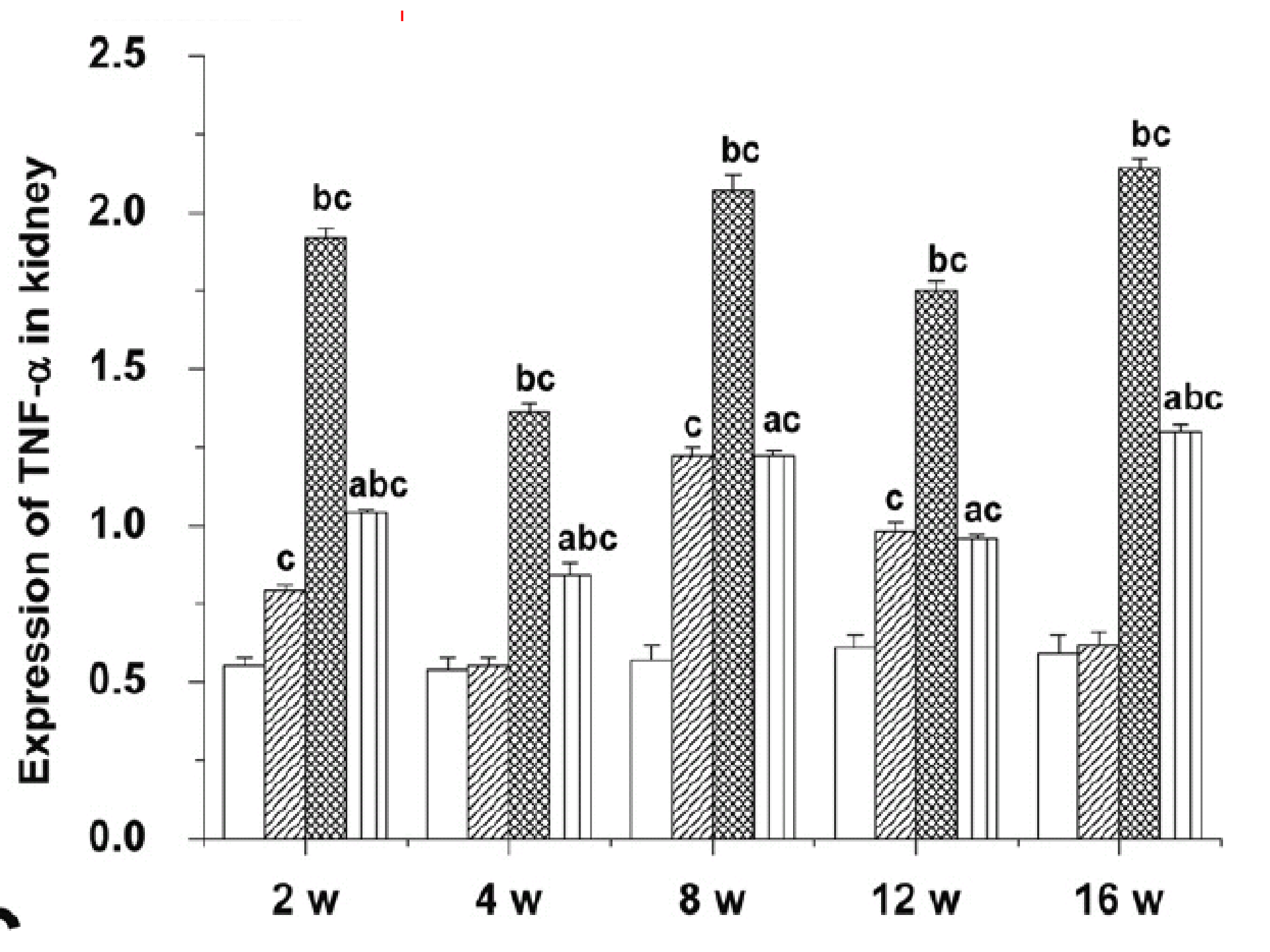


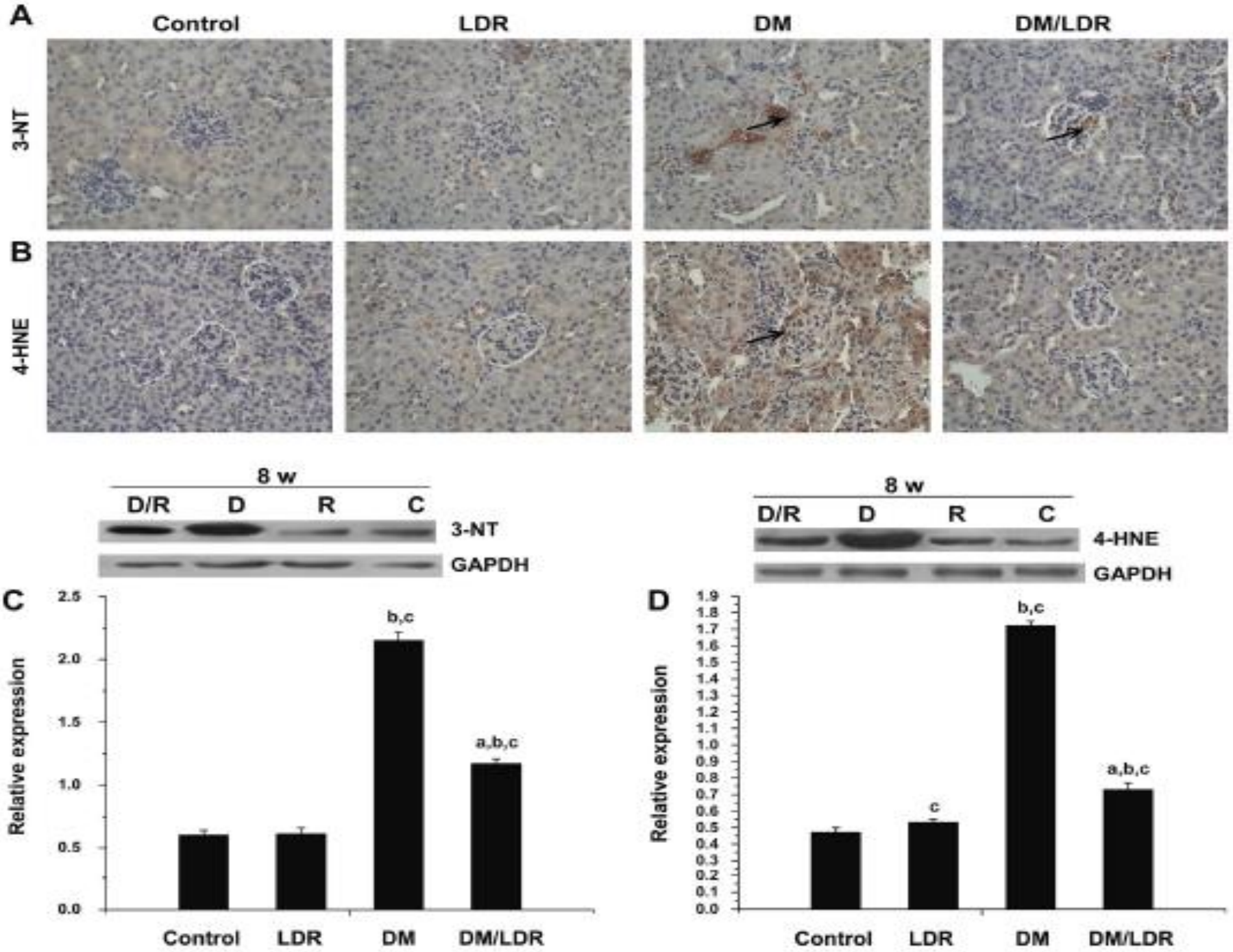
Harvest & examine cardiac inflammation and oxidative damage

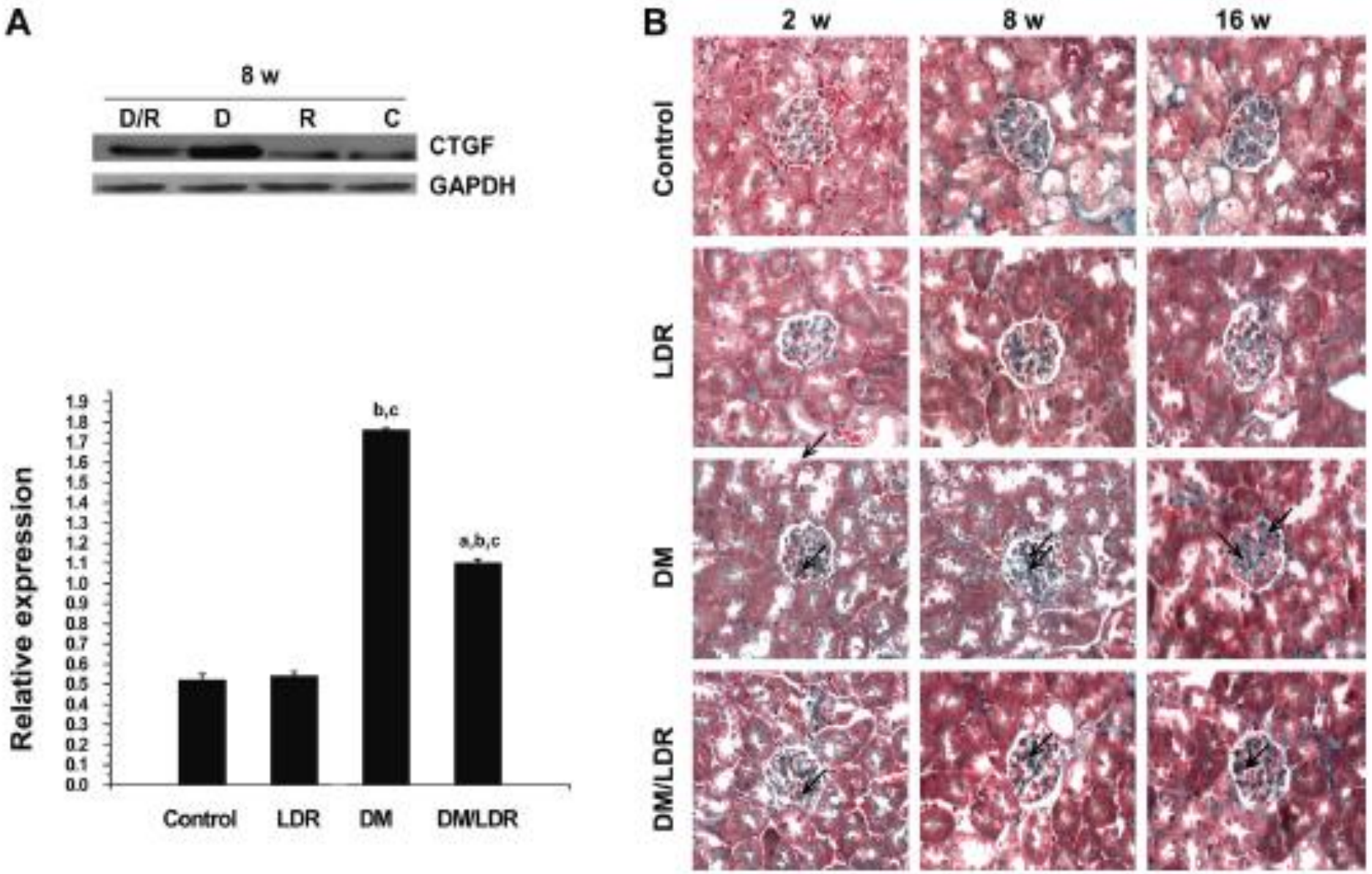

A
Blood Glucose (mmol/L)
30
25
20
15
10
5
0
bc
bc
bc
abc
bc
bc
abc
bc
bc
abc
bc
bc
abc
pre-LDR
2 w
4 w
8 w
12 w
16 w


C
Malb (mg/L)
0
5
10
15
20
25
30
35
40
pre-LDR
2 w
4 w
8 w
12 w
16 w
bc
bc
c
bc
bc
c
bc
abc
c
bc
abc
c
bc
abc
c
bc
abc


A
Control
LDR
DM
DM/LDR
Concentration of TNF-α in serum (pg/mL)
pre-LDR
2 w
4 w
8 w
12 w
16 w
B
Concentration of IL-18 in serum (pg/mL)
C
Concentration of MCP-1 in serum (pg/mL)
D
Concentration of ICAM-1 in serum (ng/mL)


Expression of TNF-α in kidney
2.5
2.0
1.5
1.0
0.5
0.0
c
bc
abc
bc
abc
c
bc
ac
c
bc
ac
bc
abc
2 w
4 w
8 w
12 w
16 w


A
Control
LDR
DM
DM/LDR
3-NT
B
4-HNE
8 w
D/R
D
R
C
3-NT
GAPDH
8 w
D/R
D
R
C
4-HNE
GAPDH
C
Relative expression
2.5
2.0
1.5
1.0
0.5
0.0
b,c
a,b,c
Control
LDR
DM
DM/LDR
D
Relative expression
1.9
1.8
1.7
1.6
1.5
1.4
1.3
1.2
1.1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
b,c
c
a,b,c
Control
LDR
DM
DM/LDR



Zhang C et al. *Am J Physiol. Endoc & Metab*. **2009, 297: 1366-1377.**

RADIATION RESEARCH 176, 356–365 (2011)
0033-7587/11 $15.00

DOI: 10.1667/RR2559.1

Suppressive Effects of Continuous Low-Dose-Rate γ Irradiation on Diabetic Nephropathy in Type II Diabetes Mellitus Model Mice

Takaharu Nomura,[a] Xiao-Han Li,[b] Hiromitsu Ogata,[c] Kazuo Sakai,[a] Takashi Kondo,[d] Yasuo Takano[b] and Junji Magae[a,1]

[a] *Radiation Safety Research Center, Nuclear Technology Research Laboratory, Central Research Institute of Electric Power Industry, 2-11-1 Iwado Kita, Komae, Tokyo 201-8511, Japan;* [b] *Department of Diagnostic Pathology, Graduate School of Medical and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama, Toyama 930-0194, Japan;* [c] *National Institute of Public Health, 2-3-6 Minami, Wako, Saitama 351-0197, Japan; and* [d] *Department of Radiological Sciences, Graduate School of Medical and Pharmaceutical Sciences, University of Toyama, 2630 Sugitani, Toyama, Toyama 930-0194, Japan*

Nomura, T., Li, X–H., Ogata, H., Sakai, K., Kondo, T., Takano, Y. and Magae, J. Suppressive Effects of Continuous Low-Dose-Rate γ Irradiation on Diabetic Nephropathy in Type II Diabetes Mellitus Model Mice. *Radiat. Res.* 176, 356–365 (2011).

It has been proposed that the development of diabetic nephropathy is caused in large part by oxidative stress. We previously showed that continuous exposure of mice to low-dose-rate γ radiation enhances antioxidant activity. Here, we studied the ameliorative effect of continuous whole-body irradiation with low-dose-rate γ rays on diabetic nephropathy. Ten-week-old

INTRODUCTION

The prevalence of type II diabetes is increasing worldwide. Diabetic complications involving retina, glomeruli, peripheral nerves, cardiovascular tissues, wound healing and pregnancy are serious lethal symptoms in adult diabetic patients. Nephropathy, characterized by impaired microvessels and excessive deposition of extracellular matrix (ECM) in the glomerular mesangium and tubulointerstitium, is a common cause of end-stage renal failure. The development of diabetic nephropathy is seen in up to roughly 30% of all type II

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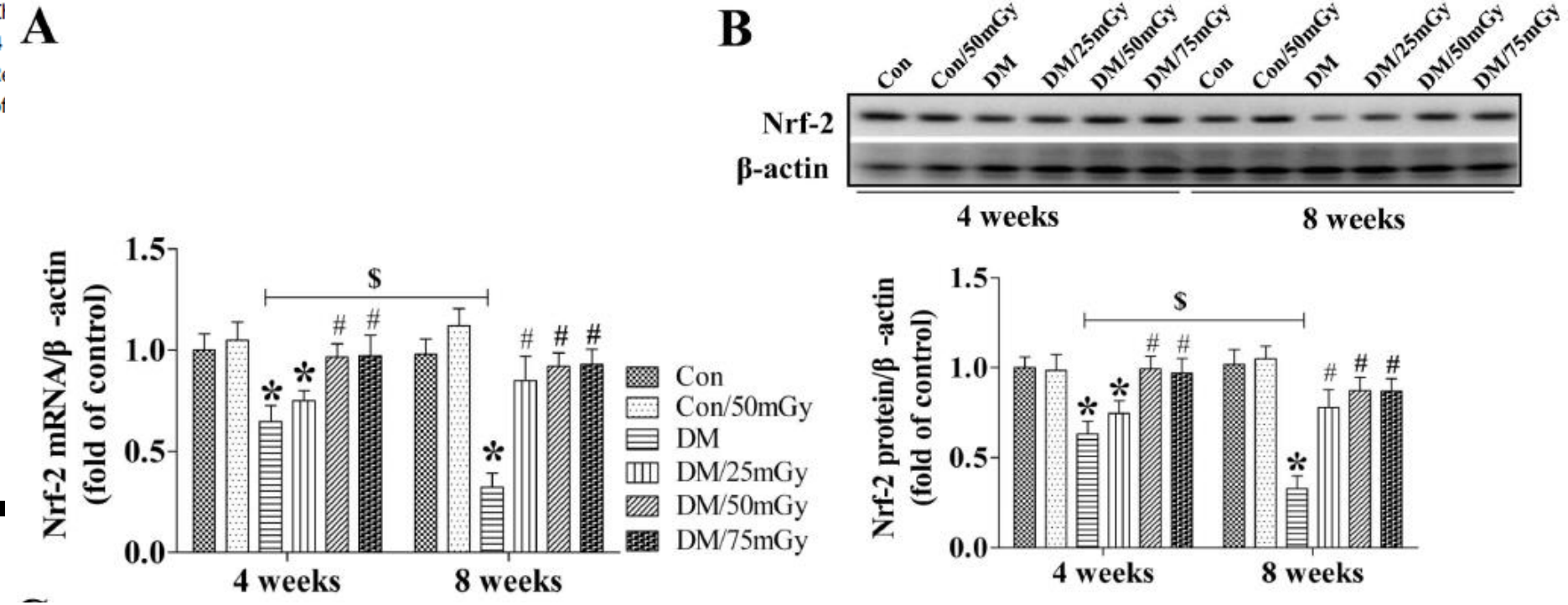
PLOS ONE

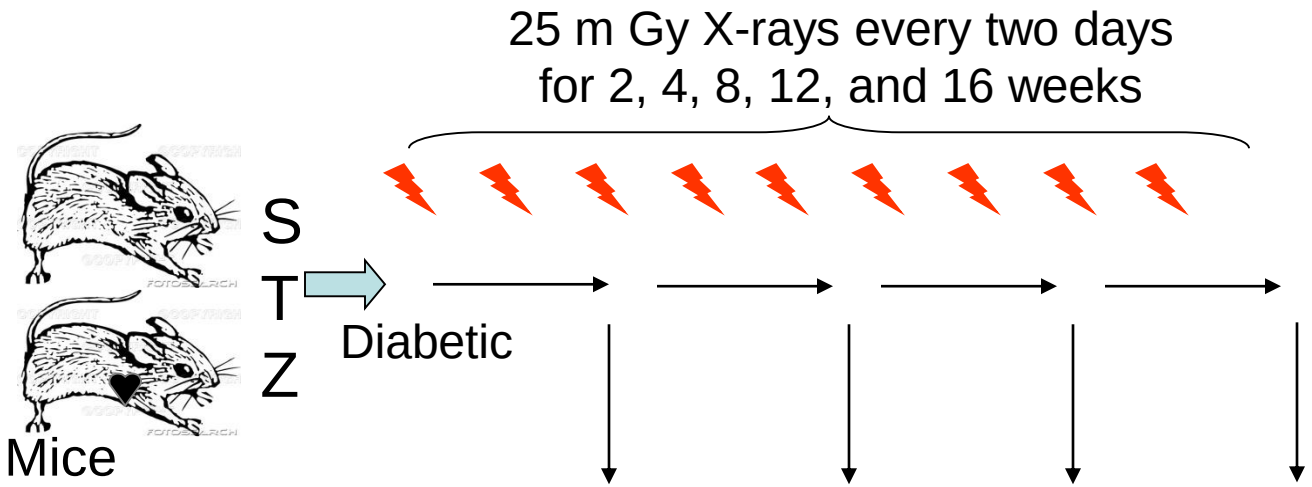
Multiple Low-Dose Radiation Prevents Type 2 Diabetes-Induced Renal Damage through Attenuation of Dyslipidemia and Insulin Resistance and Subsequent Renal Inflammation and Oxidative Stress

Minglong Shao[1,2,3], Xuemian Lu[3], Weitao Cong[2,4], Xiao Xing[1,5], Yi Tan[2,6], Yunqian Li[7], Xiaokun Li[2,4], Litai Jin[2,4], Xiaojie Wang[4], Juancong Dong[1], Shunzi Jin[1]*, Chi Zhang[2,3]*, Lu Cai[2,6]

1 School of Public Health of Jilin University, Changchun, China, 2 Chinese-American Research Institute for Diabetic Complications, Wenzhou Medical University, Wenzhou,



LDR's prevention of cardiac inflammation and damage



Harvest & examine cardiac inflammation and oxidative damage

RADIATION RESEARCH 175, 307–321 (2011)
0033-7587/11 $15.00

DOI: 10.1667/RR1950.1

Attenuation of Diabetes-Induced Cardiac Inflammation and Pathological Remodeling by Low-Dose Radiation

Chi Zhang,[a,b,c] Shunzi Jin,[c,1] Weiying Guo,[d] Cai Li,[a,e] Xiaokun Li,[a,c,f] Madhavi J. Rane,[a,g] Guanjun Wang[d] and Lu Cai[a,b,d,1]

[a] *Chinese-American Research Institute for Diabetic Complications, Wenzhou Medical College, Wenzhou 325035, China;* [b] *Departments of Pediatrics and Radiation Oncology, the University of Louisville, Louisville, Kentucky 40202;* [c] *School of Public Health of Jilin University, Changchun 130021, China;* [d] *The First Hospital of Jilin University, Changchun 130021, China;* [e] *School of Pharmacy of Jilin University, Changchun 130021, China;* [f] *Key Laboratory of Biotechnology Pharmaceutical Engineering, Wenzhou Medical College, Wenzhou 325035, and Engineering Research Center of Bioreactor and Pharmaceutical Development, Ministry of Education, Jilin Agricultural University, Changchun 130118, China; and* [g] *Departments of Medicine and Biochemistry and Molecular Biology, the University of Louisville, Louisville, Kentucky 40202*

Zhang, C., Jin, S., Guo, W., Li, C., Li, X., Rane, M. J., Wang, G. and Cai, L. Attenuation of Diabetes-Induced Cardiac Inflammation and Pathological Remodeling by Low-Dose Radiation. *Radiat. Res.* 175, 307–321 (2011).

In the present study, novel preventive effects of repeated low-dose radiation exposure on diabetes-induced cardiac inflammation and cardiac damage were investigated. C57BL/6J mice were given multiple low doses of streptozotocin (STZ, 60 mg/kg × 6) to generate type 1 diabetes. A week after the last STZ injection, hyperglycemic mice were diagnosed and treated with and without whole-body low-dose radiation exposure (25 mGy X rays) once every 2 days for 2, 4, 8, 12 and 16 weeks. Diabetes

INTRODUCTION

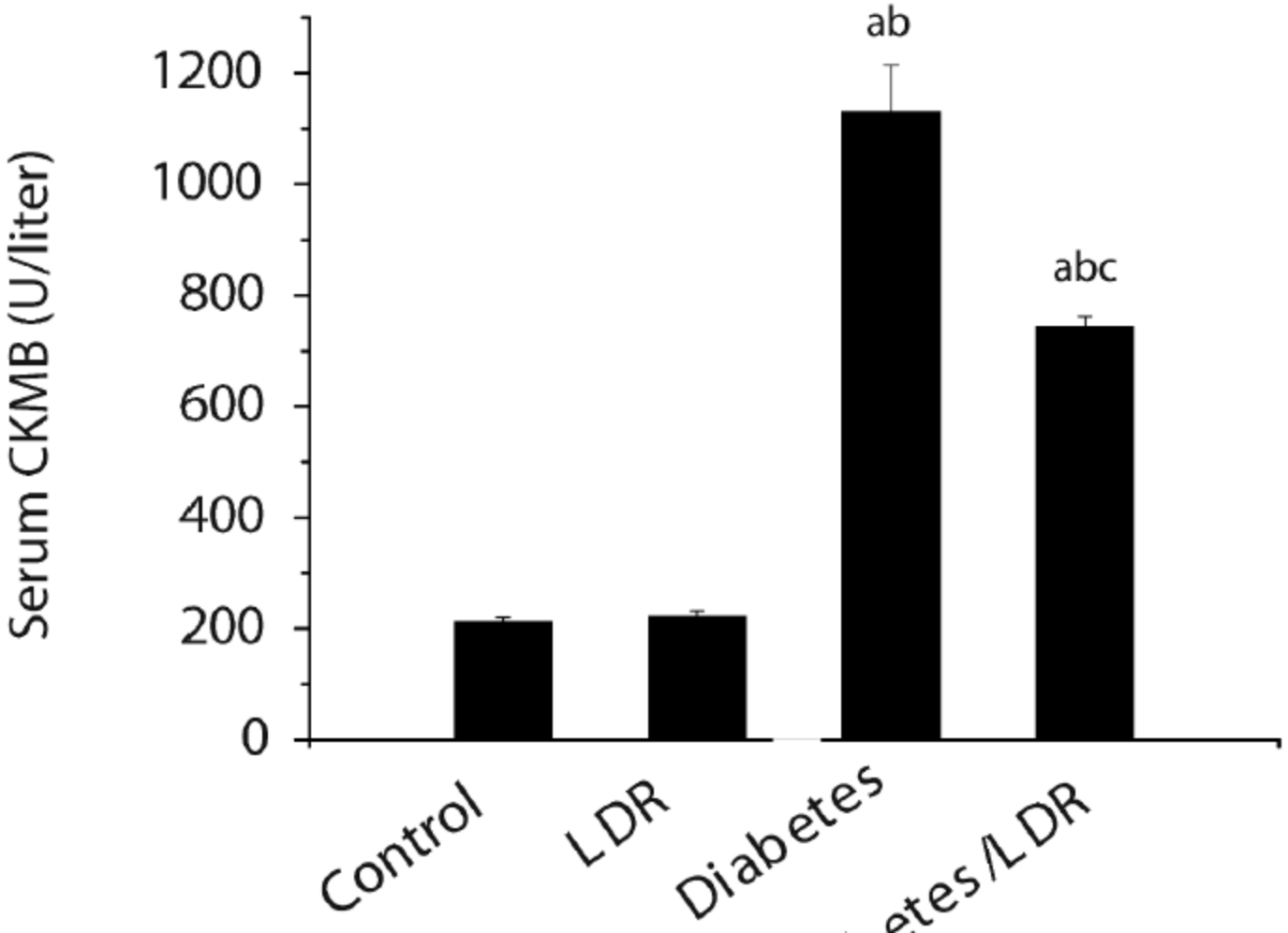
Diabetes mellitus, commonly known as diabetes, is a group of disorders characterized by a defect in the transfer of glucose from the bloodstream of a person into his or her cells. Cardiac disease is a major cause of the mortality of diabetic patients. The mechanisms responsible for the development of the diabetes-induced cardiac damage are related to multiple factors, including hyperglycemia, hyperlipidemia and inflammation (*1–3*).

Inflammatory mediators, including adipokines, chemokines, adhesive molecules and cytokines, play important roles in the development of cardiac pathogenesis in

RADIATION RESEARCH 175, 307–321 (2011)
0033-7587/11 $15.00

DOI: 10.1667/RR1950.1

Attenuation of Diabetes-Induced Cardiac Inflammation and Pathological Remodeling by Low Dose Radiation



Wang[d] and Lu Cai[a,b,d,1]

[b] Departments of Pediatrics
iversity, Changchun 130021,
Changchun 130021, China;
gineering Research Center of
China; and [g] Departments of
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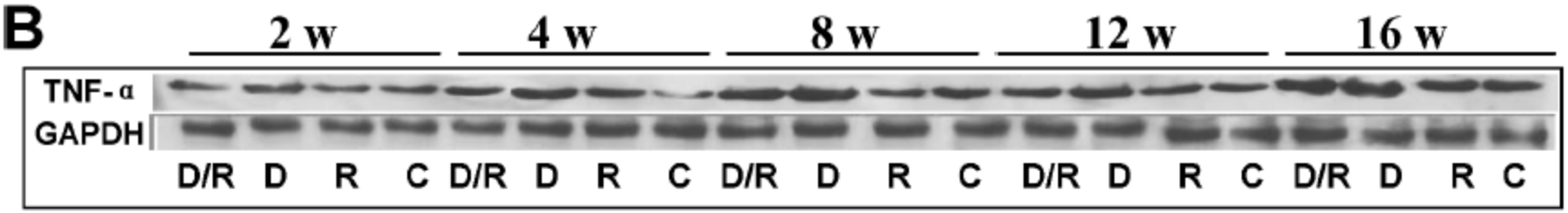
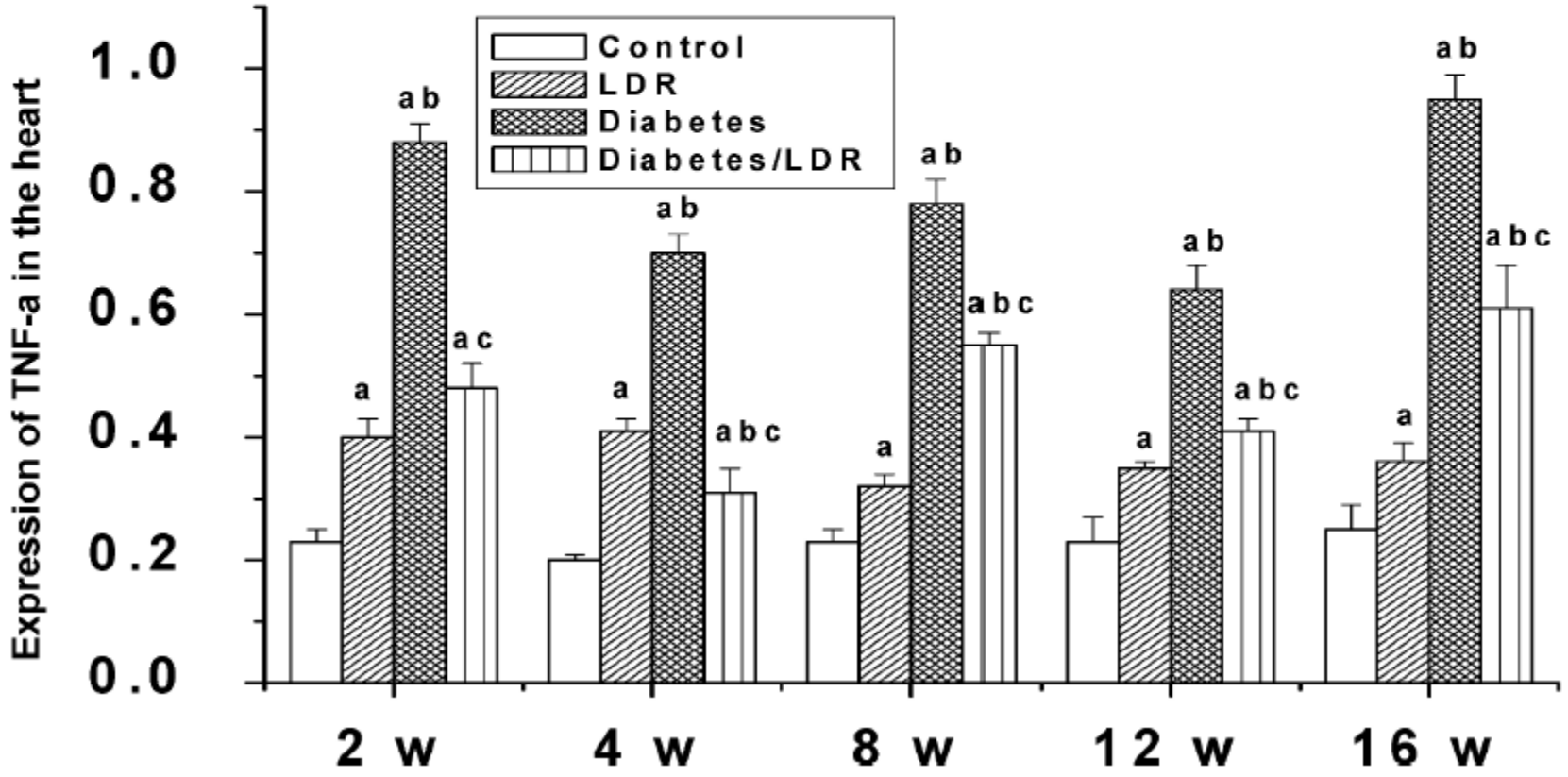
RADIATION RESEARCH 175, 307–321 (2011)
0033-7587/11 $15.00

DOI: 10.1667/RR1959.1





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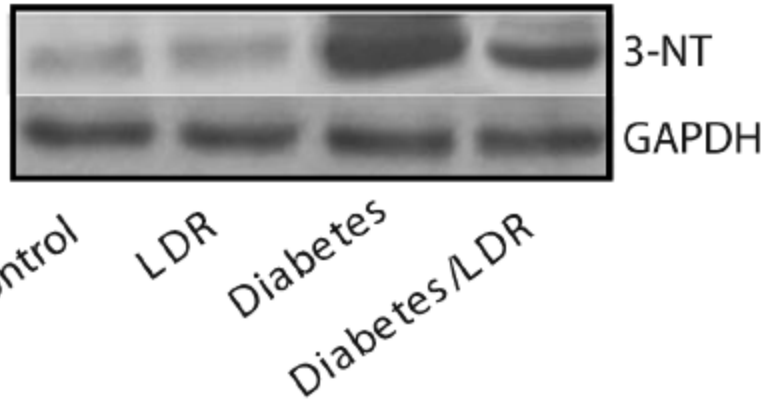

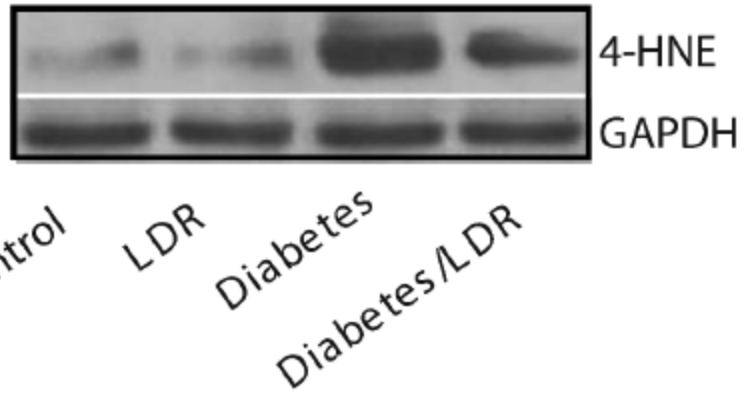

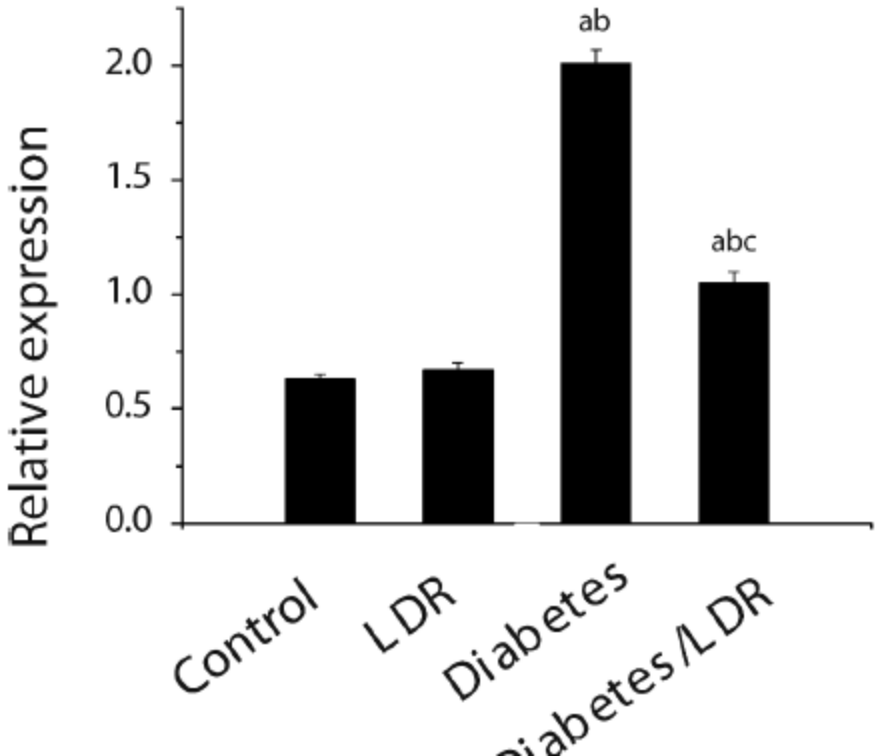

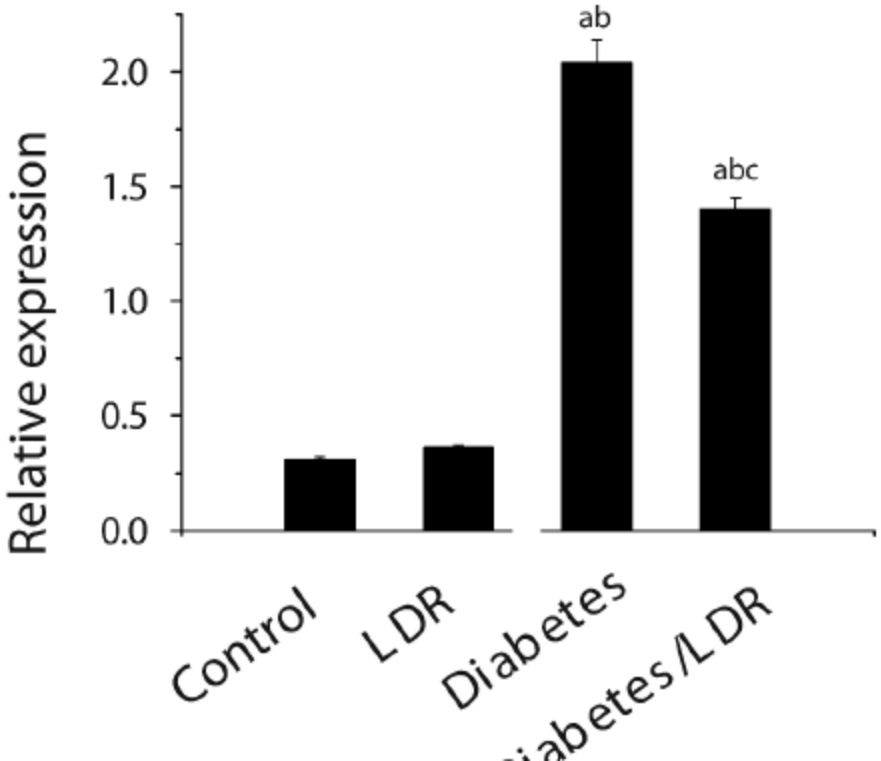

Toxicology Letters 192 (2010) 356–364

journal homepage: www.elsevier.com/locate/toxlet

Repetitive exposures to low-dose X-rays attenuate testicular apoptotic cell death in streptozotocin-induced diabetes rats

Hongguang Zhao[a,b], Songbai Xu[c], Zhicheng Wang[b], Yanbo Li[b], Wei Guo[b], Chenghe Lin[a], Shouliang Gong[b,*], Cai Li[d], Guanjun Wang[e], Lu Cai[e,f,g,**]

[a] Nuclear Medicine, The First Hospital of Jilin University, Changchun 130021, China
[b] Key Laboratory of Radiobiology, Ministry of Health, School of Public Health, Jilin University, 1163 Xinmin Street, Changchun 130021, China
[c] Neurosurgery, The First Hospital of Jilin University, Changchun 130021, China
[d] Department of Experimental Pharmacology and Toxicology, Pharmacy School, Jilin University, Changchun 130021, China
[e] Hematology and Radiation Oncology, The First Hospital of Jilin University, Changchun 130021, China
[f] Department of Pediatrics, University of Louisville, Louisville 40202, USA
[g] Department of Radiation Oncology, University of Louisville, Louisville 40202, USA

ARTICLE INFO

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Apoptotic cell death
Adaptive response
Male germ cells
Streptozotocin-induced diabetes

ABSTRACT

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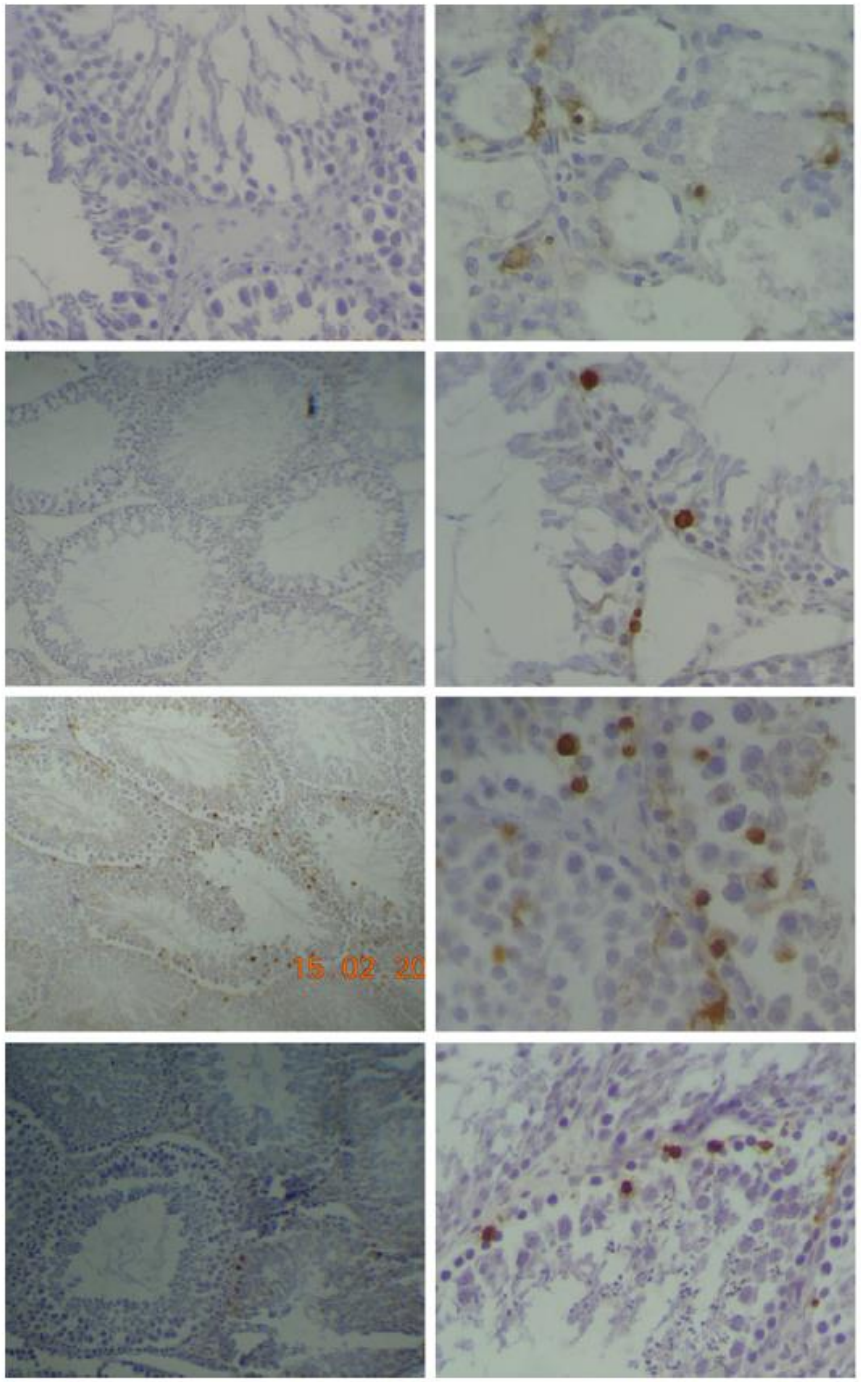
induced
ecreased
mitochondrial potential and increased expressions of Bax mRNA and protein. All these changes were significantly attenuated in certain extends by repetitive exposures to LDR. To investigate the mechanisms by which LDR attenuates diabetes-induced testicular apoptotic cell death, serum sex hormone (testosterone, luteinizing hormone and follicle stimulating hormone) levels, and both serum and testic-

LDR's prevention of diabetes-induced testicular apoptosis

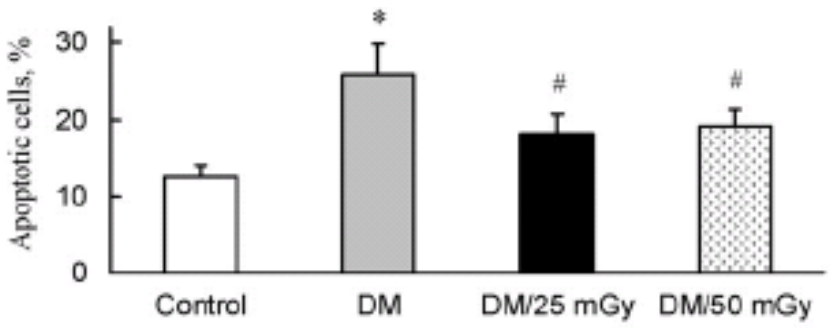


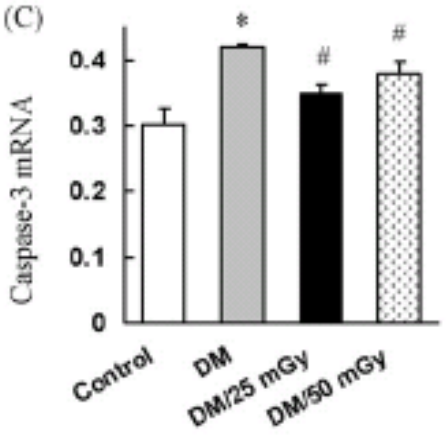
Negative/ positive staining controls

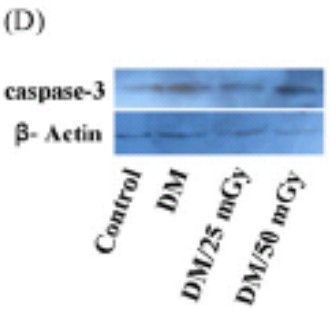
Control (10 x/40 x)

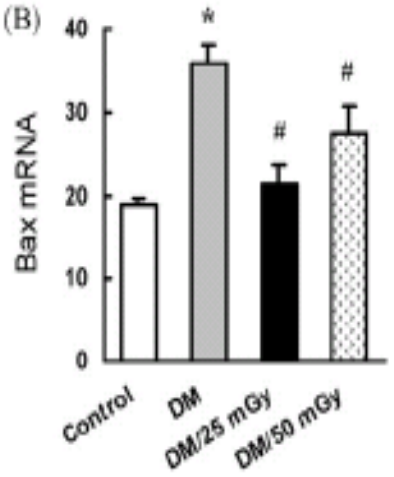
DM (10 x/40 x)

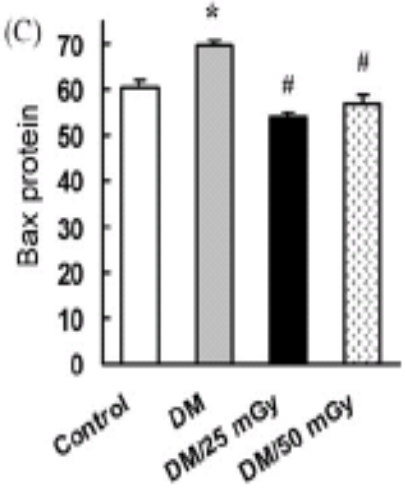
DM/25mGy (10 x/40 x)

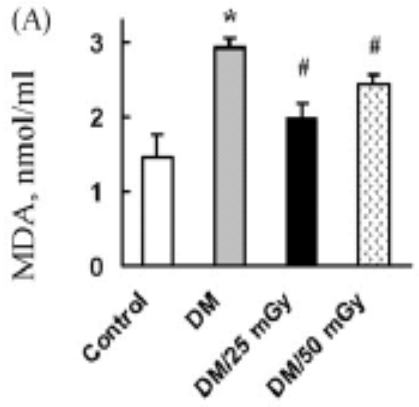


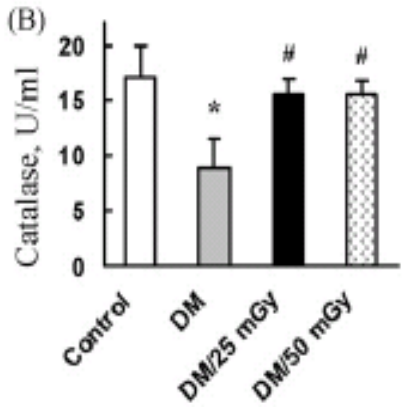


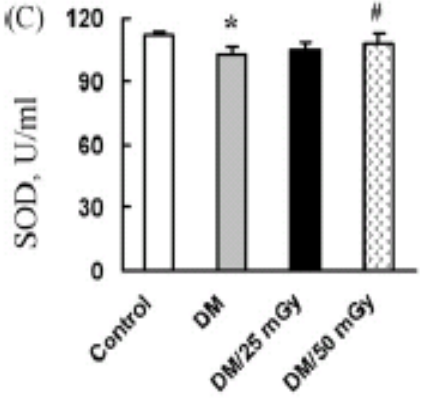


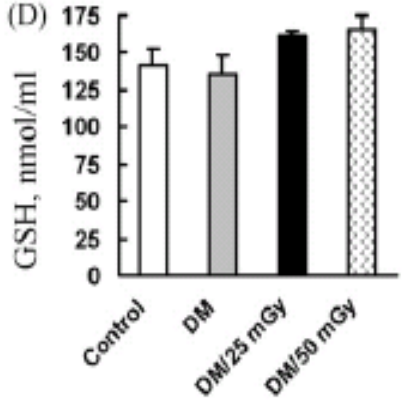


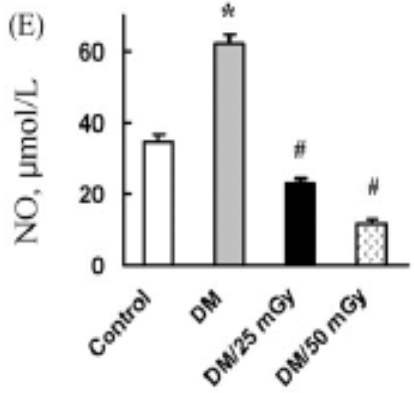


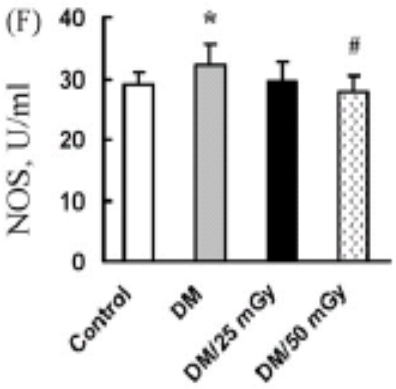


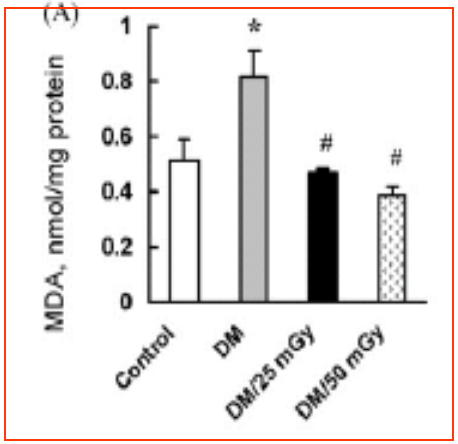


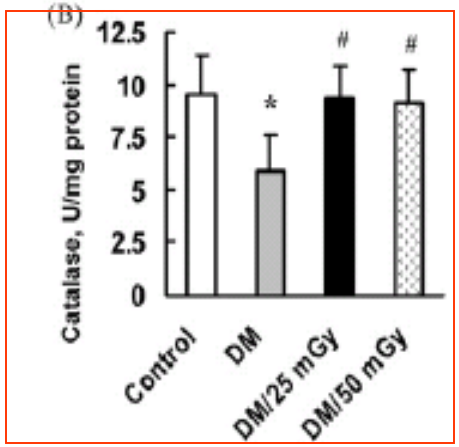


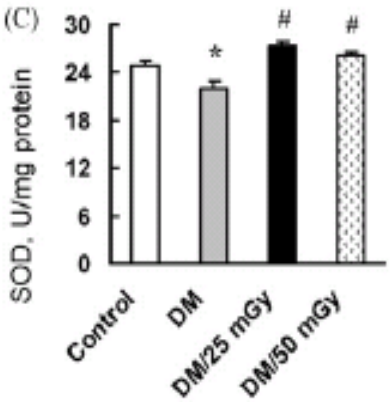


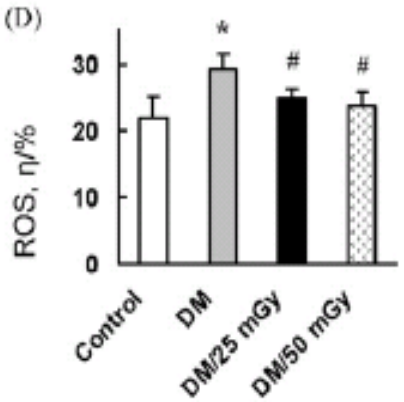


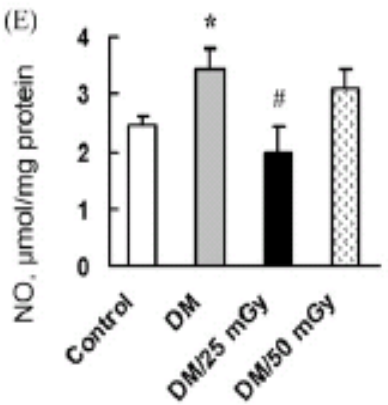


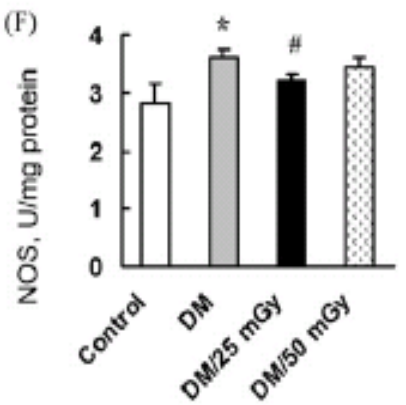












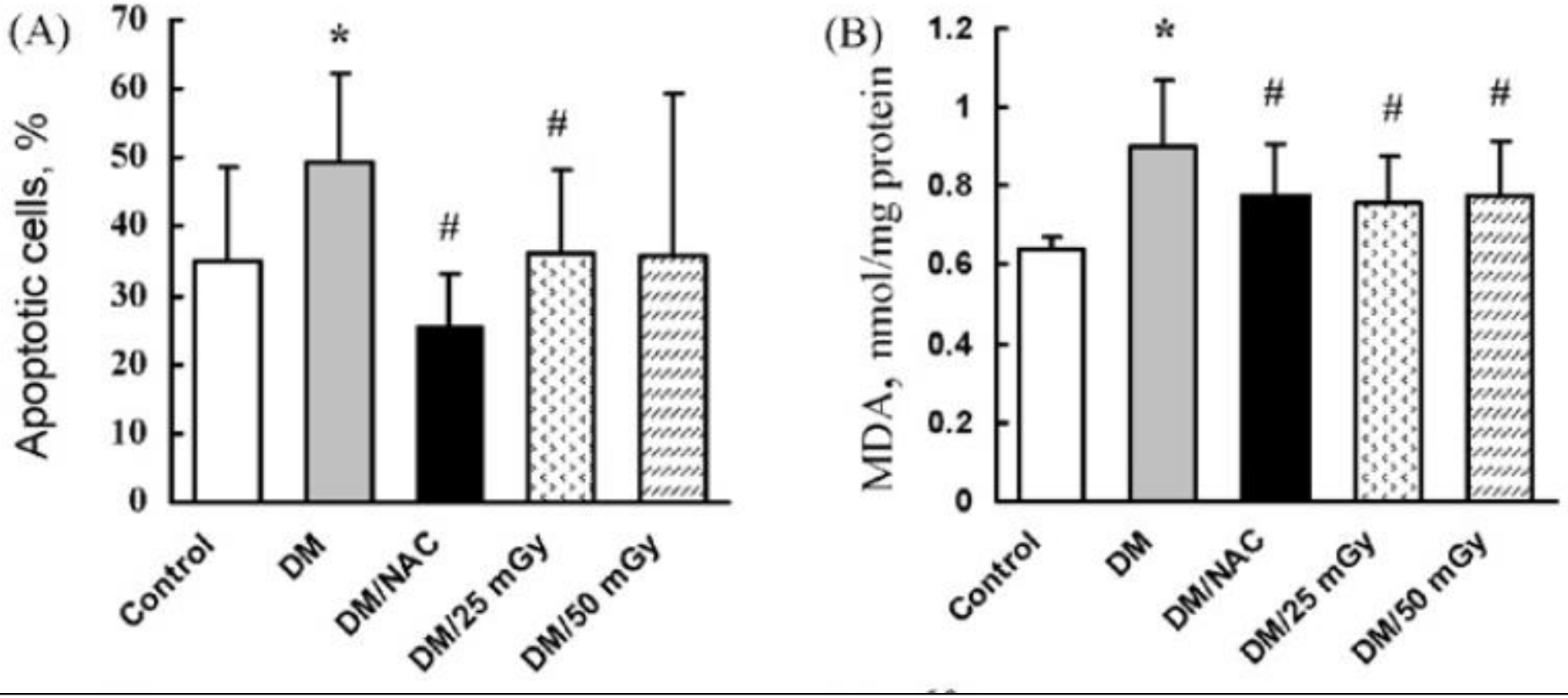
Serum/testicular

STZ-induced diabetes:

- No treatment
- LDR
- NAC

X 4 wks

Age-matched controls



J Korean Med Sci 2006; 21: 500-5
ISSN 1011-8934

Low Dose Radiation Overcomes Diabetes-induced Suppression of Hippocampal Neuronal Cell Proliferation in Rats

We investigated the effect of low dose radiation on diabetes induced suppression of neurogenesis in the hippocampal dentate gyrus of rat. After 0.01 Gy, 0.1 Gy, 1 Gy and 10 Gy radiation was delivered, the dentate gyrus of hippocampus of streptozotocin (STZ)-induced diabetic rats were evaluated using immunohistochemistry for 5-bromo-2-deoxyuridine (BrdU), caspase-3, and terminal deoxynucleotidyl transferase-mediated nick end-labeling (TUNEL) staining. The number of BrdU positive cells in the non-diabetic rats, diabetic rats without radiation, diabetic rats with 0.01 Gy radiation, diabetic rats with 0.1 Gy radiation, diabetic rats with 1 Gy radiation and diabetic rats with 10 Gy radiation were 55.4 ± 8.5/mm^2, 33.3 ± 6.4/mm^2, 67.7 ± 10.5/mm^2, 66.6 ± 10.0/mm^2, 23.5 ± 6.3/mm^2 and 14.3 ± 7.2/mm^2, respectively. The number of caspase-3 positive cells was 132.6 ± 37.4/mm^2, 378.6 ± 99.1/mm^2, 15.0 ± 2.8/mm^2, 57.1 ± 16.9/mm^2, 191.8 ± 44.8/mm^2 and 450.4 ± 58.3/mm^2, respectively. The number of TUNEL-positive cells was 24.5 ± 2.0/mm^2, 21.7 ± 4.0/mm^2, 20.4 ± 2.0/mm^2, 18.96 ± 2.1/mm^2, 58.3 ± 7.9/mm^2, and 106.0 ± 9.8/mm^2, respectively. These results suggest low doses of radiation paradoxically improved diabetes induced neuronal cell suppression in the hippocampal dentate gyrus of rat.

Key Words : *Radiation; Hippocampus; Diabetes Mellitus*

Jin Oh Kang, Sang-Ki Kim, Seong-Eon Hong, Taeck-Hyun Lee*, Chang-Ju Kim*

Departments of Radiation Oncology and Physiology*, School of Medicine, Kyung Hee University, Seoul, Korea

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Address for correspondence
Jin-Oh Kang, M.D.
Department of Radiation Oncology, Kyung Hee University Hospital, 1 Hoiki-dong, Dongdaemun-gu, Seoul 130-702, Korea
Tel : +82.2-958-8664, Fax : +82.2-962-3002
E-mail : kangjino@khmc.or.kr

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0033-7587/13 $15.00

DOI: 10.1667/RR3140.1

Low-Dose Radiation Exposure and Protection Against Atherosclerosis in *ApoE*$^{-/-}$ Mice: The Influence of *P53* Heterozygosity

R. E. J. Mitchel,[a,1] M. Hasu,[b,c] M. Bugden,[a] H. Wyatt,[a] G. Hildebrandt,[d] Y-X. Chen,[c] N. D. Priest[a] and S. C. Whitman[b,c,2]

[a] *Radiological Protection Research and Instrumentation Branch, Atomic Energy of Canada Limited, Chalk River, Ontario, Canada;* [b] *Departments of Pathology and Laboratory Medicine and Cellular and Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada;* [c] *Vascular Biology Group, University of Ottawa Heart Institute, Ottawa, Ontario, Canada; and* [d] *Department of Radiotherapy, University Hospital, Rostock, Germany*

Mitchel, R. E. J, Hasu, M., Bugden, M., Wyatt, H., Hildebrandt G., Chen Y-X., Priest N. D. and Whitman S. C. Low-Dose Radiation Exposure and Protection Against Atherosclerosis in *ApoE*$^{-/-}$ Mice: The Influence of *P53* Heterozygosity. *Radiat. Res*. 179, 190–199 (2013).

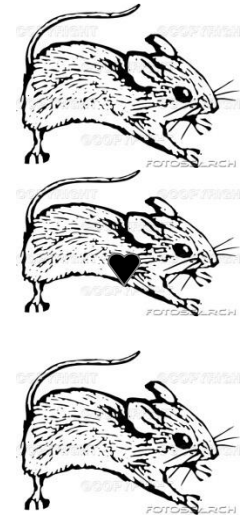
We recently described the effects of low-dose γ-radiation exposures on atherosclerosis in genetically susceptible (*ApoE*$^{-/-}$) mice with normal *p53* function. Doses as low as 25 mGy, given at either early or late stage disease, generally protected against atherosclerosis in a manner distinctly nonlinear with dose. We now report the influence of low doses (25–500 mGy) on atherosclerosis in *ApoE*$^{-/-}$ mice with reduced *p53* function (*Trp53*$^{+/-}$). Single exposures were given linear response with dose for human populations is probably unwarranted.

INTRODUCTION

Analyses of mortality in the Japanese atomic bomb survivors have raised concern about the effect of radiation on noncancer disease death rates, due to a statistically significant increase of these with radiation dose (*1, 2*). Similarly, increases for heart disease were statistically significant for doses above about 0.5 Sv (*3*) but it is unclear from the human data whether radiation exposure at doses below 0.5 Gy are associated with an increased risk of

Does LDR also have certain therapeutic effects on diabetes-complications?

LDR's therapeutic effect on diabetic wound healing



S
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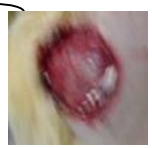
Rats

60 days

Diabetic



75 m Gy X-rays for 5 days, 2 day break & 5 days …

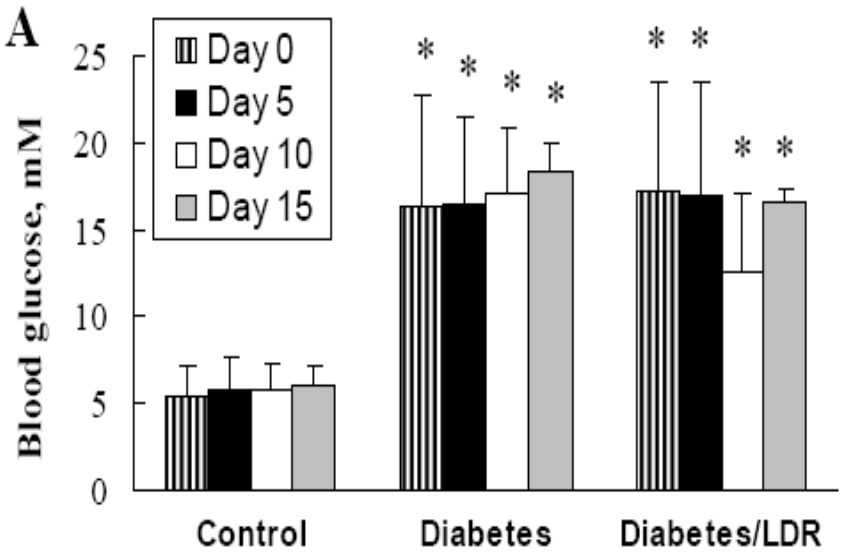
day 5 10 15

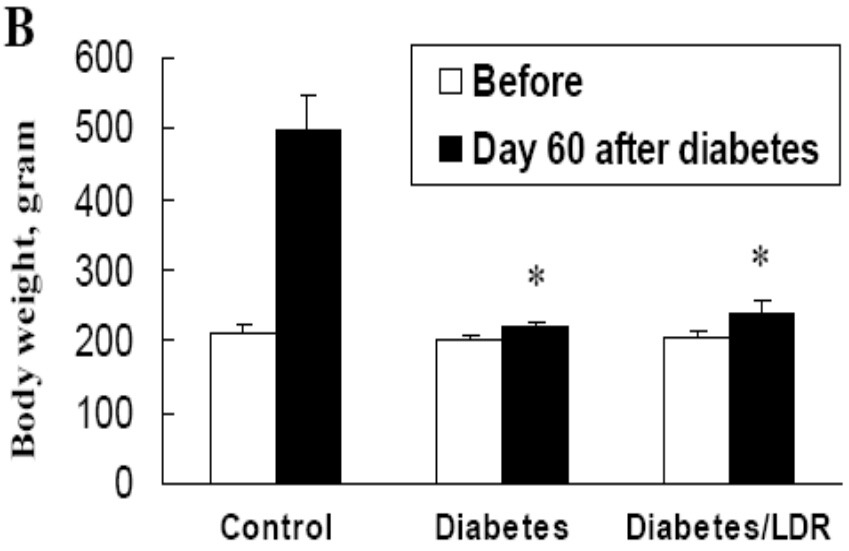
Non-diabetic mice with skin wound

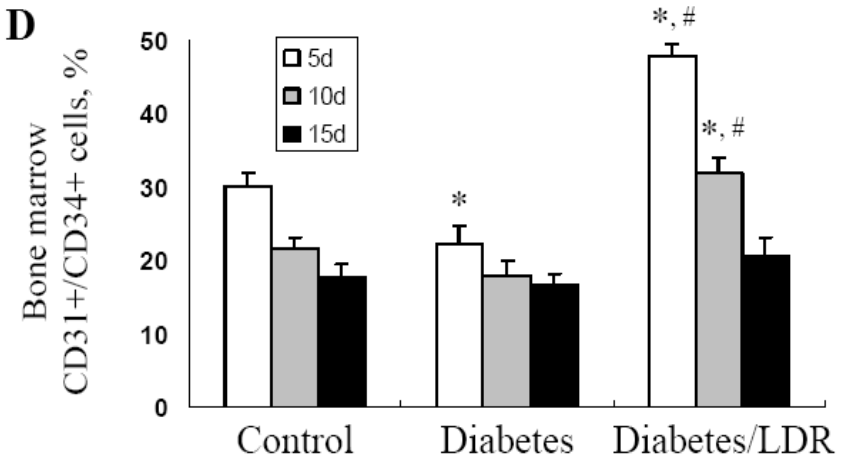
Diabetic mice with skin wound

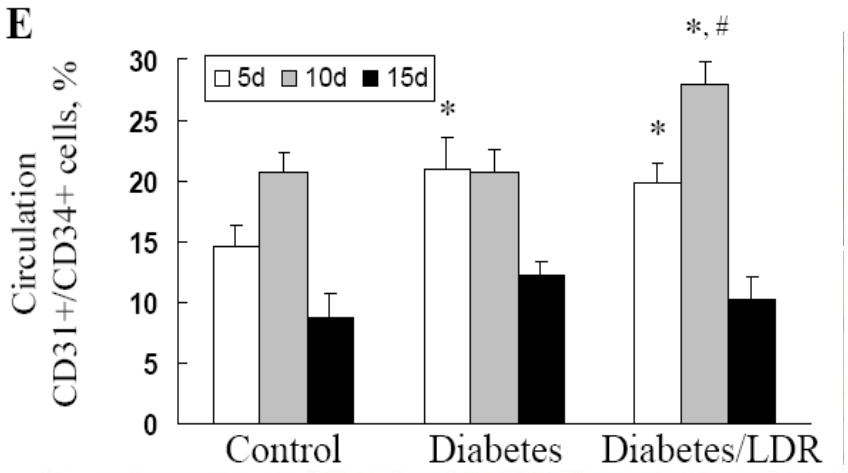
Diabetic mice with skin wound/LDR

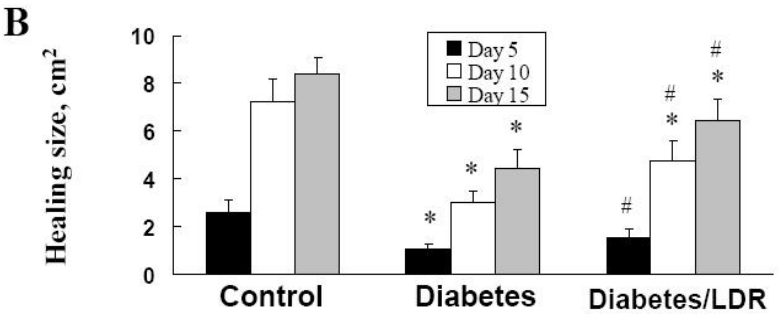
Compare











Guo W et al. *Radiation Res* 2010

Exp Hematol. 2004 Nov;32(11):1088-96.

Low-dose radiation (LDR) induces hematopoietic hormesis: LDR-induced mobilization of hematopoietic progenitor cells into peripheral blood circulation.

Li W, Wang G, Cui J, Xue L, Cai L.

D

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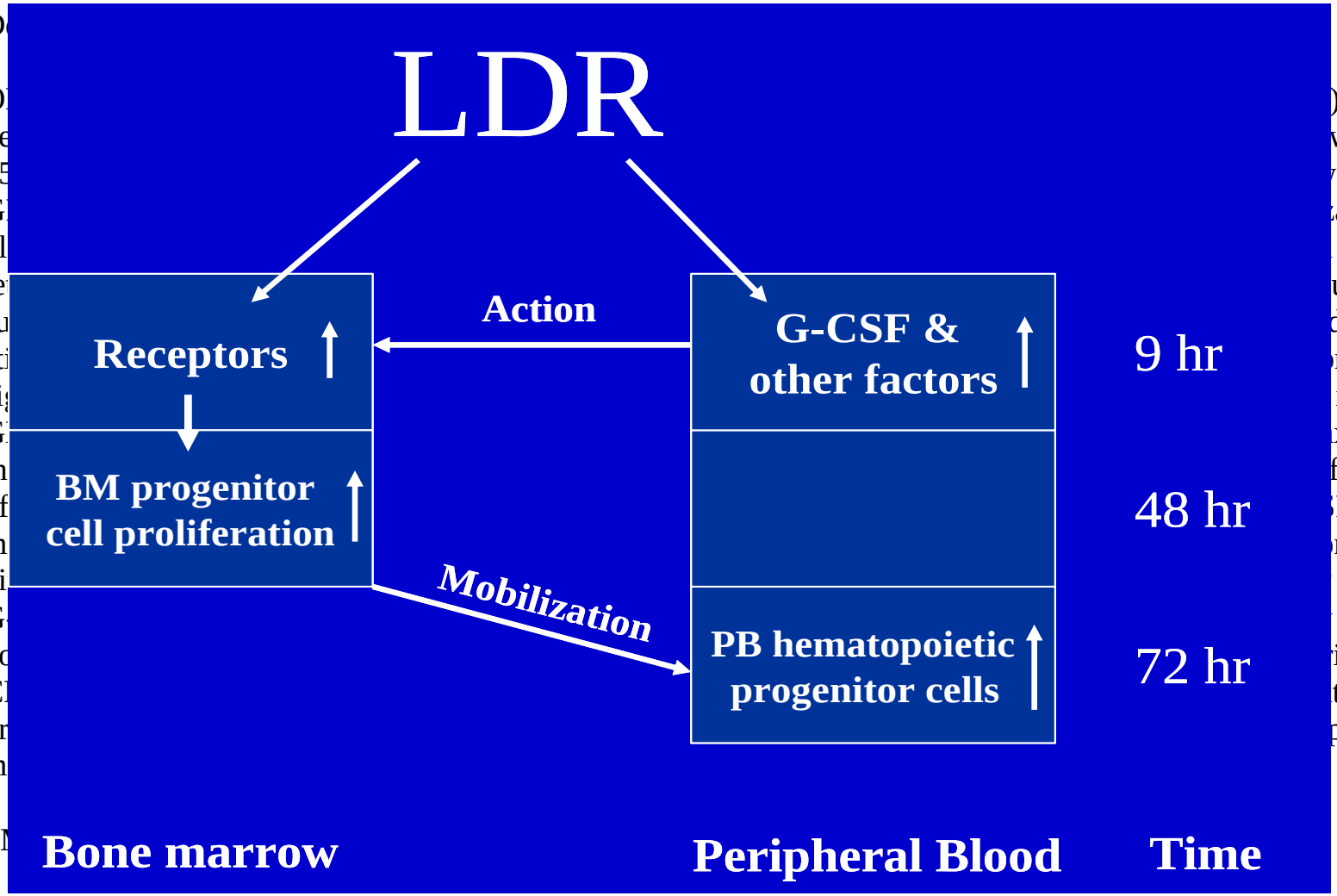

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Summary

- LDR prevents type 1 diabetes, and type 2 diabetes.
- LDR can prevent diabetes-induced renal and cardiac renal inflammation and damage
- LDR can prevent diabetes-induced testicular damage.
- LDR can prevent diabetes-induced neuronal damage, and atherosclerosis
- More importantly, LDR provides a therapeutic effect on diabetic wound healing.

- **LDR/LDR-induced hormesis and adaptive response**
- **LDR preventive effects on various injuries**
- **Diabetes/Diabetic complications**
- **Possible mechanisms**
- **Current debates for the risks & benefits**

Possible mechanisms

J. Radiat. Res., 48, 113–120 (2007)

Regular Paper

Whole Body Exposure to Low-dose Gamma Radiation Promotes Kidney Antioxidant Status in Balb/c Mice

Chander Mohan PATHAK#, Pramod Kumar AVTI, Surender KUMAR, Krishan Lal KHANDUJA and Suresh Chander SHARMA*

Antioxidant status/Kidney/Low-dose γ-irradiation/Radiation hormesis.

We examined the effect of whole body low-dose γ-irradiation on the status of the antioxidant defense system in the rodent kidneys at different time intervals. Young male Balb/c mice were exposed to whole body radiation from a ^{60}Co source at doses of 10, 25 and 50 cGy (48.78 cGy/min). Antioxidant status and lipid peroxidation were estimated in the kidneys at 4, 12 and 24 h after irradiation. Lipid peroxidation increased between 33% and 49% and reduced glutathione between 12% and 47% at 12 h at different radiation doses. Reduced glutathione level remained significantly ($p < 0.05$) elevated even at 24 h after irradiation to 25 cGy. Superoxide dismutase activity also increased by 37% at 12 h on exposure of animals to all the doses up to 50 cGy. Catalase activity increased significantly at 12 h on exposure to 10 cGy and 50 cGy. Interestingly, glutathione peroxidase activity increased by 31% at 4 h and subsequently returned to control levels at 24 h after exposure to 50 cGy. Glutathione reductase activity increased by 10–12% at 12 h after exposure to 25 cGy and 50 cGy. The results suggest that the whole body exposure of animals to

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Hindawi Publishing Corporation
Oxidative Medicine and Cellular Longevity
Volume 2012, Article ID 291087, 12 pages
doi:10.1155/2012/291087

Research Article

Low-Dose Radiation Activates Akt and Nrf2 in the Kidney of Diabetic Mice: A Potential Mechanism to Prevent Diabetic Nephropathy

Xiao Xing,[1,2] Chi Zhang,[2,3] Minglong Shao,[1,2] Qingyue Tong,[4] Guirong Zhang,[4] Cai Li,[5] Jie Cheng,[5] Shunzi Jin,[1] Jisheng Ma,[6] Guanjun Wang,[5] Xiaokun Li,[1,2] and Lu Cai[2,3,7]

[1] *School of Public Health of Jilin University, Changchun 130021, China*
[2] *Chinese-American Research Institute for Diabetic Complications, Wenzhou Medical College, Chashan University Park, Wenzhou 325035, China*
[3] *The Department of Pediatrics, School of Medicine, The University of Louisville, 570 South Preston Street, Baxter I Building Suite 304F, Louisville, KY 40059, USA*
[4] *Norman Bethune College of Medicine, Jilin University, Changchun 130021, China*
[5] *Norman Bethune First Hospital, Jilin University, Changchun 130021, China*
[6] *Engineering Research Center of Bioreactor and Pharmaceutical Development, Jilin Agricultural University, Changchun 130118, China*
[7] *Departments of Pharmacology and Toxicology and Radiation Oncology, School of Medicine, The University of Louisville, 570 South Preston Street, Baxter I Building Suite 304F, Louisville, KY 40059, USA*

Correspondence should be addressed to Xiaokun Li, xiaokunli@163.net and Lu Cai, l0cai001@louisville.edu

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Cell Death and Differentiation (2014) 21, 836–844

www.nature.com/cdd

Low-dose radiation exposure induces a HIF-1-mediated adaptive and protective metabolic response

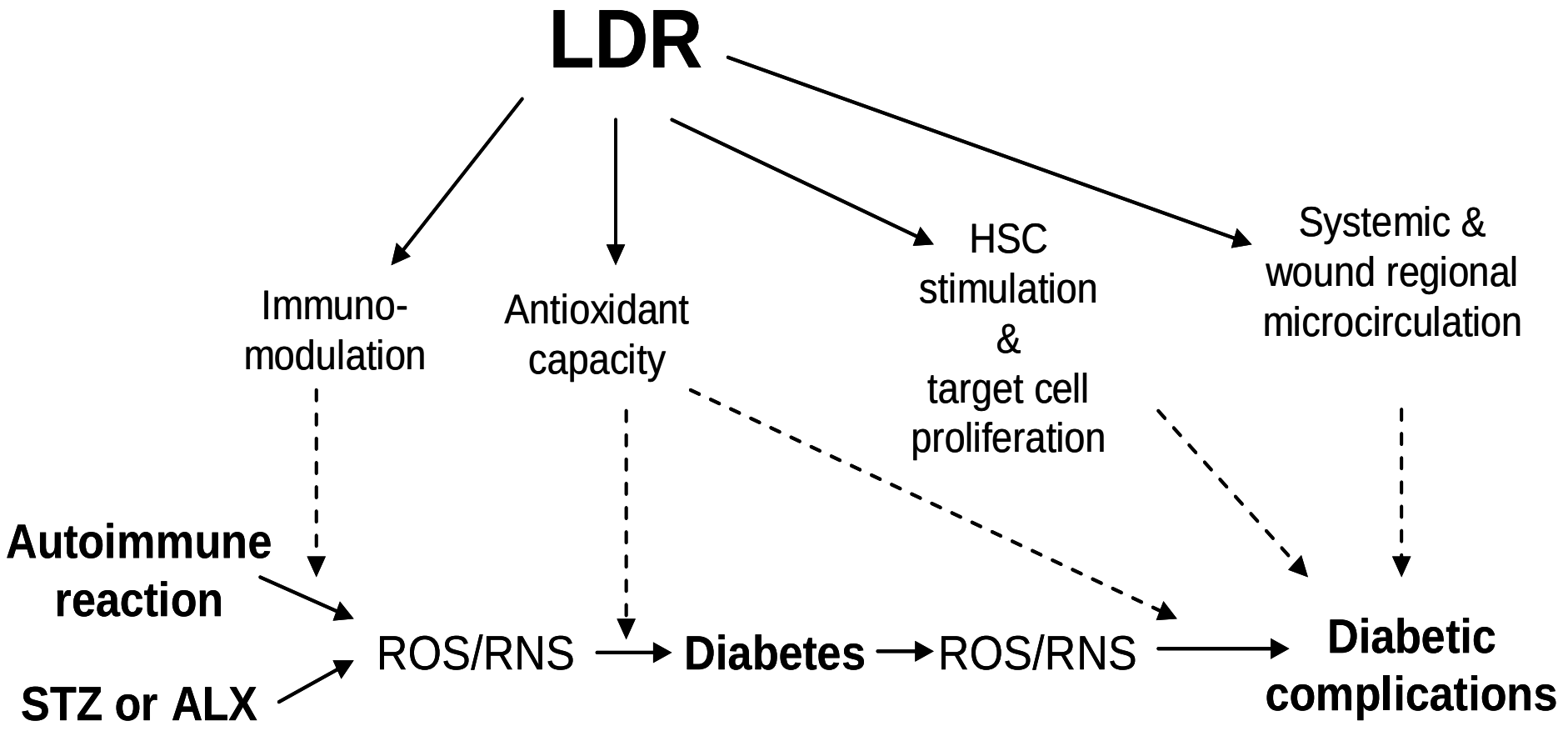
R Lall[1,5], S Ganapathy[2,5], M Yang[2], S Xiao[1,6], T Xu[1], H Su[1], M Shadfan[1], JM Asara[3,4], CS Ha[1], I Ben-Sahra[2], BD Manning[2], JB Little[2] and Z-M Yuan*[,2]

Because of insufficient understanding of the molecular effects of low levels of radiation exposure, there is a great uncertainty regarding its health risks. We report here that treatment of normal human cells with low-dose radiation induces a metabolic shift from oxidative phosphorylation to aerobic glycolysis resulting in increased radiation resistance. This metabolic change is highlighted by upregulation of genes encoding glucose transporters and enzymes of glycolysis and the oxidative pentose phosphate pathway, concomitant with downregulation of mitochondrial genes, with corresponding changes in metabolic flux through these pathways. Mechanistically, the metabolic reprogramming depends on HIF1α, which is induced specifically by low-dose irradiation linking the metabolic pathway with cellular radiation dose response. Increased glucose flux and radiation resistance from low-dose irradiation are also observed systemically in mice. This highly sensitive metabolic response to low-dose radiation has important implications in understanding and assessing the health risks of radiation exposure.
Cell Death and Differentiation (2014) **21,** 836–844; doi:10.1038/cdd.2014.24; published online 28 February 2014

The advance of diagnostic imaging and interventional radiology has attracted growing interest in the biological effects of low-dose (⩽0.1 Gy) ionizing radiation (IR).[1] Because of a lack of means for the direct assessment of such low-dose IR exposure, however, there are great uncertainties about its health risk.[1] Currently, a linear no-threshold (LNT) dose model is used to predict low-dose

Biological tissues consist of ~75% water by weight. A major fraction of IR exposure induces hydrolysis resulting in different types of reactive oxygen species (ROS).[9] IR induces the production of ROS proportional to its dose. High-dose IR induces an excess amount of ROS that can overwhelm the cellular antioxidant capacity causing oxidative stress and damages.[9] When mildly increased, ROS, however, can

Possibilities for LDR's prevention of diabetes and diabetic complications



Possible mechanisms

- LDR stimulate the target tissue antioxidant capacity (Nrf2 & its down stream antioxidants)
- LDR stimulate glucose metabolisms
- LDR stimulate stem cells to injured tissue to recover the damage tissue
- LDR may stimulate the enzymes that were introduced by Dr. David Lefer, to generate H_2S
- ***Hormesis***, and ***adaptive response***

- **LDR/LDR-induced hormesis and adaptive response**
- **LDR preventive effects on various injuries**
- **Diabetes/Diabetic complications**
- **Possible mechanisms**
- **Current debates for the risks & benefits**

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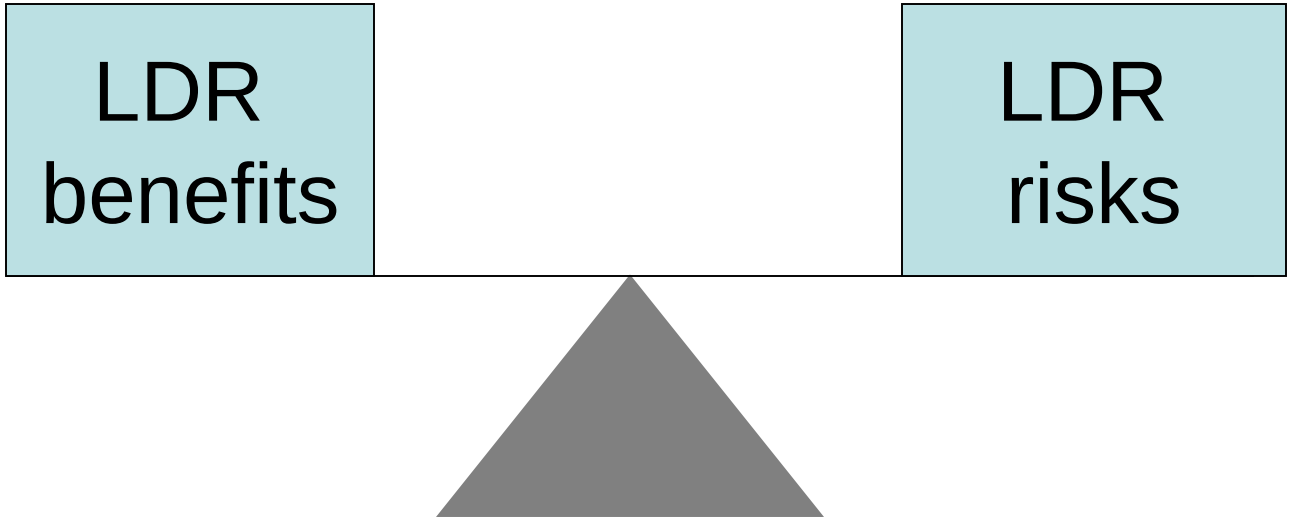
Is it potentially applied in clinics? How to balance?



Clinical Lung Cancer, Vol. 16, No. 2, 152-5 © 2015

Original Study

Lung Cancer Hormesis in High Impact States Where Nuclear Testing Occurred

Steven Lehrer, Kenneth E. Rosenzweig

Abstract

Hormesis is a favorable biological response to low toxin exposure. In the case of radiation, large doses are

Conclusion

Our analysis adds to the body of evidence suggesting that the LNT model of radiation carcinogenicity in lung cancer might not be correct. Low-level radiation exposure might protect against lung cancer rather than cause it.

in Radiation Exposure in the United States (2000). Data on high- and normal-impact states were from the National Radiation Exposure Screening & Education Program (RESEP). Congress passed the Radiation Exposure Compensation Act Amendments of 2000, creating RESEP, to help thousands of people diagnosed with cancer and other diseases

Am J Physiol Endocrinol Metab 299: E137, 2010;
doi:10.1152/ajpendo.00247.2010.

Letter to the Editor: Low-dose whole body irradiation: a potential therapeutic modality?

Chander M. Pathak and Krishan L. Khanduja

Department of Biophysics, Post Graduate Institute of Medical Education and Research, Chandigarh, India

TO THE EDITOR: The recent article published by Zhang et al. (11) in this Journal is indeed very interesting and has great clinical relevance with far-reaching consequences. This appears to be the first detailed report that suggests that multiple exposures to

In another interesting study, Yamaoka and Komoto (10) reported that the Misasa Hot Spring treatment with radon significantly improved vasodilation and alleviated diabetic symptoms. In animal studies, WB-LDR has been found not

It is clear that none of the medications used in clinical practice is absolutely nontoxic. Therefore, there is a need to evaluate the application of non-invasive technology like WB-LDR to be as realistic and parallel as is done for other therapeutic modalities. If WB-LDR really can play a critical role in the prevention or treatment of certain disorders such as diabetes, then we should accept the same without any radiation phobia in the mind.

Current Research

But since the turn of the current century, researchers have been reexamining radiation hormesis, applying LDR treatment in various disease settings in laboratory animals.

Various studies in mice have found that exposure to low-dose radiation protects against the effects of subsequent exposure to mid-lethal doses of X-rays, minimizing DNA damage and mortality.

A similar effect has been observed when the radiation is received in utero. Exposure of pregnant mice to "Chernobyl radiation" (doses and types of radiation encountered by the bulk of humans living near the site of the 1986 nuclear accident), did not harm the newborn mice. And the researchers found that later doses of radiation did less harm to the mice's DNA health and levels of white blood cells than were seen in untreated mice.

Within the last few years, LDR has shown promise in combating the complications of diabetes. Studies have found that diabetic rats show faster wound healing when dosed with low levels of radiation. And other rodent experiments have found that radiation at very low doses can prevent kidney damage, one of the most common long-term complications of diabetes.