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Alzheimer's disease and low-dose radiation therapy: A new hope

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Abstract

The concept of low-dose radiation (LDR)-induced hormetic responses was initially observed approximately 70 years ago and systematically reviewed along with the discovery of LDR-induced adaptive responses in a cytogenetic *in vitro* study in 1980s. By the end of the 1990s, discussions regarding the potential applications of LDR-induced hormesis and adaptive responses for preventing or treating chronic diseases, such as Alzheimer's disease (AD) had taken place. Until 2016, reports on radiotherapy for the subjects with AD and for genetic AD model mice were published. Subsequently, several preclinical studies with animal models of AD and clinical studies in AD subjects were conducted. A significant milestone was achieved with the online availability of a new Systematic Review based on qualified publications from these preclinical and clinical studies. This mini-review provides a concise historical introduction to LDR-induced hormesis and adaptive responses with discussion of AD radiotherapy with either LDR or relatively high dose radiation. Highlights of this Systematic Review cover promising outcomes, challenges, and new questions, followed by discussion of potential mechanisms.

Keywords

Alzheimer's disease; Low-dose radiation; Radiation adaptive response; Radiation hormesis

1. Introduction

The concept of low-dose radiation (LDR)-induced hormesis responses was first observed 70 years ago in a mouse study demonstrating life-span extension through exposure to very low doses of radiation.[1] Lucky[2] later synthesized early-year studies to highlight

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the potential stimulating effects, or hormesis, induced by LDR. Subsequently, additional insightful reviews followed.[3] Both reviews serve as crucial and comprehensive summaries of early studies on the biological effects of LDR.[2,3] A pivotal moment in research on LDR-induced hormesis emerged, in 1984, with the introduction of the concept of LDR-induced adaptive response.[4] This refers to the hormetic mechanisms induced by LDR, rendering cells or organisms highly resistant to damage upon subsequent exposure. Subsequent to this groundbreaking concept, numerous studies have delved into this area. For instance, the BELLE (Biological Effects of Low-Level Exposure) Newsletter featured a collection in 1999 titled "Adaptive Response Induced by Low Levels of Radiation" (TOC,7.3 (dose-response.org)). This compilation explored five key topics, including the question of whether the induction of adaptive response could be manipulated for medical and other benefits.[5] The intention was to offer a clear and reasonable perspective on the various appropriate uses of radiation in our lives, emphasizing how these applications significantly contribute to improving our health and quality of life.

As a part of this collection, the author of this mini-review contributed a review titled "*Research of the adaptive response induced by low-dose radiation: where have we been and where should we go?*".[6] This review was only one among the seven reviews invited, to evaluate, "Whether LDR-enhanced activity of antioxidants in the brain could protect brain cells from oxidative damage is a new field to investigate." The author cited a human epidemiological study revealing a lower incidence of Alzheimer's disease (AD) in high background radioactivity areas (HBRA) compared to controls (4.39 % *vs.* 4.95 %); however, since this 1999 publication, there have been no additional reports on the prevalence of AD in the HBRA versus control areas. Subsequent studies on potential LDR therapy (LDRT) for AD with different dose ranges of radiation have advanced significantly, yielding promising outcomes in both animal preclinical and human clinical studies (see below).

2. The early studies on AD and LDRT

Cuttler et al.[7] reported the first case of LDRT in the subject with AD.The case of an 81-year-old female subject with advanced AD was not significantly controlled. She received ~40 mGy computed tomography (CT) scans for times over a period of three months, which partially restored cognition, memory, speech, movement, and appetite. Based on the significant improvement, the subject continually received CT scans every couple of months, until her 83rd birthday.[8,9] Basically, she received CT at 40 mGy 12 times with an accumulated dose of 0.48 Gy over a period of 32 months, and symptoms were significantly improved by several objective evaluations. Although this was only one case and was without quantitative methods, it was encouraging.[7–9] Therefore, Cuttler et al.[10] has moved forward to conduct a pilot clinical phase I trial (NCT03597360) with an additional four subjects with AD.

Meanwhile, the effects of radiotherapy for animal models of AD were also reported by Marples et al.[11] providing the first evidence that radiotherapy reduced amyloid plaques. Compared to the dose of a CT scan (40 mGy/fraction, 0.48 Gy in total over 32 months) for the subjects with AD, different exposures of radiation were used: single exposure (5, 10, and 15 Gy) and fractionated exposure (10 × 1 Gy, 5 × 2 Gy and 10 × 2 Gy) for mice with

AD.[11] The possibility was suggested to further reduce radiation doses to ensure a sufficient disease control with less potential side effects, such as low dose (<1 Gy) weekly fractionated radiation therapy (RT).[12]

3. A milestone for AD and LDRT, highlighting recent systemic review by Kaul et al

Since 2016, several studies on LDRT for subjects with AD and animal models of AD were reported from several groups, including those mentioned above, which were included in the excellent systemic review by Kaul et al.[13] This review included 12 preclinical studies with animal models of AD and 4 clinical observations after LDRT, published before July 1, 2023, and was available online on November 30, 2023.[13]

The authors of the review realized the fact that pathophysiological hallmarks of AD include extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles. Early studies also demonstrated a role of neuroinflammation in the progression of the disease. Clinical trials and animal studies using LDRT have shown therapeutic potential for AD. This systematic review was conducted based on the limited human and animal studies published until July 1, 2023, as well as registered clinical trials describing outcomes for RT in the treatment of AD, following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As outlined in Fig. 1, this review selected a total of 16 publications (12 pre-clinical studies with animal models and 4 clinical studies in patients) from an initial search yielded 993 articles, based on their based on the pre-specified inclusion and exclusion criteria.[13]

For the preclinical studies with animal models, Karl et al.[13] have described each of these 16 studies in detail to summarize these studies in 6 groups, which included (1) Primary aim; (2) Disease status; (3) Radiation regime; (4) Subjects; (5) Time between RT and sacrifice or analysis; (6) Outcomes that were further divided into several columns: (a) Outcome parameters; (b) Results; (c) Conclusions. Most of the preclinical studies used mouse models of AD, few used rats and only one used mini-pigs.

For the clinical studies, the authors described four studies separately to summarize the six specific questions with a similar table as used for the preclinical studies. For outcomes, the reports for the first patient by Cuttler et al.[7–9] showed remarkable improvements in cognition, speech, movement, and appetite during the first four scans, but not later. In the second study with four subjects by Cuttler et al.[10] three also showed remarkable qualitative improvements in cognition and behavior, but not the fourth. In contrast, for those subjects exposed to 2 Gy for 5 or 6 times did not show improvement as reported by Cuttler et al.[7–9] although some measures showed mild improvement. However, none of the trials or studies described significant (>grade 2) toxicity, as summarized by Kaul et al.[13]

As a milestone review, the authors also discussed three major issues, summarized in Fig. 1: (1) Proposed mechanisms of action, which remains unclear even though several studies proposed the reduction of neuroinflammation and amyloid through LDRT; (2) Open questions on AD pathophysiology; (3) Challenges in trial design and dose finding.

These questions and challenges are well discussed and will be important for the further investigation on the LDRT for AD, which are referred to in the original review[13] for the readers who are interested in the detail.

Therefore, this is an excellent systemic review and an important milestone for the study of radiotherapy for AD, not only to provide summarized evidence of LDRT on AD, but also to provide several open questions and challenges to accelerate research with human cases and animal models.

4. Additional discussions

After highlighting this milestone systemic review, we wish to specifically discus more about (1) the doses used for these studies on AD and (2) potential mechanisms responsible for the improvement of AD in responses to LDRT based on this systemic review and other recent publications.

4.1. Definition of LDR and doses used for LDRT

Because LDR effects have been extensively investigated as mentioned above, a long-term strategic and prioritized agenda for LDR research has been recently developed by the U.S. Congress in partnership with the U.S. Department of Energy called on the National Academies of Sciences, Engineering, and Medicine (NASEM).[14,15] The definition of LDR doses has been discussed and accepted by NASEM, which defined LDR as the dose level less than 100 mGy or low-dose rates less than 5 mGy per h.[14] Accordingly, radiation at doses between 0.1 and 1.0 Gy and higher 1.0 Gy is considered as intermediate/moderate and high doses, respectively.[16,17] However, this LDR concept has been mainly used or discussed for the research regarding the risk assessment, particularly in the field of LDR-induced hormesis and adaptive response since radiation increase of solid cancer risk at less than 100 mGy has been inconsistent and extensively debated. In contrast, cancer radiotherapy aims at killing cancer cells, therefore, clinical radiotherapy doses usually are very high (40–60 Gy) even though these high doses are delivered in multiple fractions, generally at 1.8 or 2 Gy per daily fraction.[18] Therefore, radiation at 1–2 Gy is often counted as low-dose therapeutic radiation.[19,20]

The dose levels of LDRT for AD used so far were significantly different among these studies, from 40 mGy to 2000 mGy (2 Gy), as mentioned above. For instance, among the 4 clinical studies, two of them were done in Canada by Cuttler et al.[7–10] using 40 mGy/fraction with 12 exposures during the 32 months. One study was done in the USA by Rogers et al.[21] with 2 Gy/fraction daily for 5 d, and the last one was done in the Korea by Kim et al.[22] using 0.5 Gy/fraction for 6 times in two weeks (3 times/week). Cuttler et al.[7–10] reported remarkable improvements in cognition, speech, movement, and appetite during the first four scans, but not later. For the second study by Cuttler et al.[10] three of with four subjects also showed remarkable qualitative improvements in cognition and behavior, but not the fourth. In contrast, for those subjects exposed to 2 Gy for 5 fractions or 0.5 Gy for 6 fractions did not show improvement as reported by Cuttler et al.[7–10] although some measures showed mild improvements. Therefore, these clinic studies suggest no remarkable

better outcome compared to exposure to multiple CT (40 mGy). However, none of the trials or studies described significant toxicity, as stated by Kaul et al.[13]

Among the 12 preclinical studies, the dose levels were more complex, including a single large dose of radiation and fractionized medium-low doses. For instance, Marples et al.[11] from the USA have irradiated Cg-tg AD-prone mice either with single dose of 5, 10 and 15 Gy or fractioned doses of 10 × 1 Gy, 5 × 2 Gy, and 10 × 2 Gy. There were also two studiesusing high LET radiation with and without low LET radiation.[23,24] There was only one study with 0.6 Gy/fraction[25] and two studies with 1.7 Gy/fraction[26] and 1.8 Gy/fraction,[27] respectively. All the other studies[11,25,28–33] were done with 2 Gy/fraction for multi-times. In the animal models of AD, most of studies used mice, a few studies used rats, and only one study used mini-pigs. In general, all these protocols have resulted certain improvements; however, it remains difficult to state which show the best, remarkable different from others in terms of the improvements. There is also no apparently dose-dependent manner for the therapeutic effects.

4.2. Potential mechanisms for LDR hormesis and adaptive response, and AD's radiotherapy

Regarding the mechanisms responsible for the improvement of AD by LDRT, it remains too early to make conclusions due to several reasons: (1) mechanism for AD remains unclear, (2) available clinical studies for AD's LDRT remain limited; (3) Even there are relatively more preclinical studies, their conditions are not consistent and also varied among the models of AD among rats, mice, minipigs, reviewed by Kaul et al.[13] and reported by additional studies[34,35]; (4) The significant different dose ranges used for AD treatment also cause the difficult explanations of the mechanisms responsible for the improvement of AD by radiation.

Fig. 2 illustrates the major radiation biological effects, for instance radiation hormesis, adaptive response, and bystander effects induced by LDR as well as detrimental effects induced by high dose radiation.[14–20] This suggests that when exposed dose is less than 100 mGy, the cells and tissue responses are predominantly protective even though with minor damage while dose is high, the responses of the cells of exposed tissue are predominantly detrimental. In the clinical studies, there was little mechanistic investigation since there was limitation of any histopathological, cellular and molecular assays. However, in the preclinical studies, the majority showed improvement of neurological behaviors consistent with clinical studies, but also provided findings that may help understand the mechanisms responsible for the beneficial effects of LDRT in AD patients. A few aspects are discussed below.

4.2.1. Amyloid-β (Aβ) plaques—Marple et al.[11] irradiated male B6.Cg-Tg AD mice for the right half of the brain with X-rays at a single dose of 5 Gy, 10 Gy or 15 Gy (0.69 Gy/min) and sacrificed either 24 h or 2, 4 and 8 weeks later for the first cohort. A second cohort of animals was treated with three different lower-dose schedules 1 Gy × 10 fractions, 2 Gy × 5 fractions, or 2 Gy × 10 fractions. They showed: (1) Single irradiation significantly reduced Aβ plaque numbers compared to sham (left side brain) with a slightly dose-dependent effect

at 40%–60 % reduction at 15 Gy; (2) Examination at 4 wks post-fractionized irradiation, Aβ plaque numbers were significantly reduced about 50 % (1 Gy × 10 fractions), 70 % (2 Gy × 5 fractions) and 75 % (2 Gy × 10 fractions), respectively. Due to the similar effects on reduction of Aβ plaque numbers between 2 Gy × 5 fractions and 2 Gy × 10 fractions, several other subsequent studies started to use 2 Gy/d for 5 d to conduct their studies with the evidence of reducing Aβ plaque numbers in rats and mice of AD models.[28,30,32,33]

As a major component of Aβ plaques, Aβ1–42 was able to cause synaptotoxicity associated with long-term potentiation and cognitive deficits. Direct injection of human Aβ1–42 peptide into hippocampal CA1 area of adult mouse brain bilaterally resulted in an extensive neurodegeneration in the Aβ-accumulated area and CA3 in hippocampus.[36] By applying a single injection of synthetic Aβ1–42 peptide, Khan et al.[31] have developed a rat model to mimic AD. Four week later, rats were irradiated 2 Gy daily for 5 d. They found that (1) LDRT significantly decreased in amyloid deposits in brain of the Aβ1–42þIR-treated animals by histopathological analysis; (2) LDRT significantly improved neurobehavioral tests in Aβ1–42-induced memory impairment, suggesting the direct impact of Aβ plaque accumulation on the behavior.

Therefore, the mechanisms responsible for the improvement of patients with AD and transgenic animal models of AD for their neurobehavior function and histopathology remain unclear. This is mainly because it remains too early since we just learned therapeutic phenomenon in these limited clinical cases and diverse animal models. Although above proposed couple of signaling pathways, which and how some of them or all pathways play the role in the real mechanism remain unclear and needs further investigation.

4.2.2. Brain's inflammation and LDR effects—As pointed out by Kaul et al.[13] the authors of the Systemic Review, neuroinflammation is a major hallmark in AD. In the central nerves system, microglia are the main producers of pro-inflammatory cytokines, but astrocytes are also contributing. Neuro-inflammation correlates with an increase of Aβ plaque levels in AD mouse models and also with mild cognitive impairment, the proposed precursor of AD, in humans. The most recent cross-sectional study by enrolling 2743 old participants from the 2011–2014 National Health and Nutrition Examination Survey (NHANES) confirmed the strong inverse correlation between systemic inflammation markers and cognitive performance.[37] Therefore, inflammation is a promising avenue for enhancing cognitive health and mitigating age-related cognitive decline.

Marple et al.[11] irradiated male B6.Cg-Tg AD mice at 30 weeks old as introduced above. In this study, gene and proteomic finding showed significant inhibition of increased expression of glycogen synthase kinase-3 beta (GSK-3β), macrophage inflammatory protein 2 (MIP-2) and interferon gamma (INF-γ) by LDRT (2 Gy × 5 fractions). Several other preclinical studies with rodent models of AD also showed the suppression of inflammatory cytokines along with increase in anti-inflammatory cytokines.[25,27,30,33] Among inflammatory cytokines, tumor necrosis factor alpha (TNF-α), transforming growth factor beta (TGF-β) and IFN-γ are responsible for the pathogenesis of AD and, consequently may serve as diagnostic or therapeutic targets for AD neurodegeneration.[38] Increasing evidence shows that IFN-γ has a unique role in microglial activation while

priming by IFN-γ results in proliferation (microgliosis), enhanced synapse elimination, and moderate nitric oxide release sufficient to impair synaptic transmission, γ-rhythm activity, and cognitive functions; IFN-γ is also pivotal for driving Toll-like receptor-activated microglia into neurotoxic phenotypes.[39] In the brain of transgenic AD mice, reduction of increased expression of IFN-γ[11] or IFN-induced transmembrane protein 3 (IFITM3)[34] in response to LDRT at 2 Gy daily for 5 d or at chronic exposure for 112 d with accumulation of 100 mGy or 300 mGy was observed.

Recently GSK-3β was considered as a potential therapeutic target for the treatment of AD, because GSK-3β activation increases Aβ plaque and the development of neurofibrillary tangles that are involved in the disruption of material transport between axons and dendrites, leading to the loss of memory and synaptic function.[40–42] The increased expression of GSK-3β in the brain of transgenic AD mice was significantly inhibited by LDRT at 2 Gy × 5 fractions along with neuronal behavior improvement.[11] Reportedly, exposure of vascular endothelium to 3 Gy ionizing radiation activates Akt signaling to inhibit GSK-3β, which in turn promotes endothelial cell survival and capillary formation.[43] In fact, when wild type mice were exposed to whole body X-rays at either single 500 mGy or 50 mGy daily for 10 d, the hippocampus Akt expression was significantly increased in the group with 50 mGy × 10 fractions compared to control and 0.5 Gy single dose.[44] We also showed the activation of Akt in multi-organs of mice exposed to multiple 25 mGy and single dose of 75 mGy.[45,46] Interestingly in a *Drosophila* AD model, LDRT at a dose of 50 mGy suppressed AD-like phenotypes, including developmental defects and locomotive dysfunction of Aβ42-expressing flies. In addition, overexpression of phosphatase and tensinhomolog (PTEN), a negative regulator of the AKT signaling pathway, or AKT mutation strongly suppressed the beneficial effects of LDRT in Aβ42-expressing flies.[35] These results confirm that LDR suppresses Aβ42-induced cell death through regulation of the AKT signaling pathway-mediated suppression of GSK-3β, suggesting that LDR hormetic effects on the pathogenesis of Aβ42-associated AD probably via suppression of GSK-3β.

4.2.3. Anti-inflammation and anti-oxidative proteins—It is well-known that IL-10, an immunosuppressive cytokine, is counted as an important anti-inflammatory modulator of glial activation, preventing inflammation-mediated neuronal degeneration in AD pathogenesis.Under some conditions it maybe also responsible for clinical worsening.[47,48] Marple et al.[11] reported an increased trend for more IL-10 stained cells in the irradiated brains in response to LDRT; however, higher IL-10 expression in group of 1 Gy × 10 fractions than that in groups of 2 Gy × 5 fractions, and single 10 and 15 Gy was seen. Reportedly rats were exposed to whole-body γ-rays at 0.25 and 0.5 Gy, and 14 d later these rats were irradiated with another irradiation at 5 Gy. Four days post-irradiation at 5 Gy, rats were sacrificed and examined, showing that exposure to 5 Gy significant reduced blood IL-10 in control rats, but not reduced in the rats with pre-exposure to 0.25 or 0.50 Gy, accompanied by reduction of other inflammation cytokines and lipid peroxidation in the blood. LDR-induced adaptive response significantly protected from 5 Gy-induced injury, which probably was related to its preservation of IL-10 level.[49]

In addition, the protective effects by LDR via hormesis or adaptive response mechanisms on second challenge or pathogenic stress are attributed predominantly to efficient anti-oxidative

enzymes and proteins, as illustrated in Fig. 2. Rats exposed to whole body LDR at 200 mGy showed increases in the total and reduced glutathione and catalase of brains, which was more significant at early time (6 h) compared to the late time (24 h).[50] A most recent study discovered in a mouse study that the application of 300 mGy X-ray at 8 h post-injury still maintained full therapeutic effects on motor recovery in traumatic brain injury and ischemic stroke, which is most likely through LDRT-up-regulated anti--inflammatory and phagocytosis-related genes, and down-regulated key pro-inflammatory cytokine production.[51] It is well-accepted that oxidative stress and inflammatory response play crucial roles in the pathogenesis and development of AD.[52] LDR at <100 mGy and even 500 mGy have approved to increase multiple anti-oxidative enzymes and proteins, which may also play certain in the improvement of AD pathogenesis and behavior.

5. The hope for AD LDRT

In conclusion, while there is some intriguing preclinical evidence suggesting that LDR may have neuroprotective effects in the context of AD, more research is needed to establish its safety and efficacy. The potential risks associated with radiation exposure, coupled with ethical consideration, underscore the importance of rigorous scientific investigation before considering LDRT as a viable treatment option for AD. Individuals interested in the latest developments in this field should consult more recent and specialized sources for updated information. Finally, Kaul et al.[13] pointed out several challenges and further questions, which are summarized in Fig. 1. Considering these challenges and limitation of the clinical evidence, the authors also noted that the design of a larger phase II/III clinical trial is challenging, given the lack of understanding of underlying pathophysiological processes and their interaction with radiation therapy.

In fact, a phase II multicenter, prospective, single-blinded, randomized controlled trial has started to evaluate the efficacy and safety of LDRT to the whole brain using a linear accelerator in 60 subjects with mild AD, which has registered with their protocol published.[53] For this trail, the radiation dose will be given at low (40 mGy) or intermediate (0.5 Gy) per fraction as discussed above. The subjects will be randomly assigned to three groups: experimental I (40 mGy × 6 fractions), experimental II (0.5 Gy × 6 fractions) or sham group (0 Gy 6 fractions). During LDRT and follow-up visits after LDRT, possible adverse events will be assessed by interview and neurological examinations. Furthermore, the effectiveness of LDRT will be measured using neurocognitive function tests and imaging tools at 6 and 12 months after LDRT.[53]

Hopefully, this phase II clinical trial will bring more encouraging outcomes, to fulfill the hope as described in the title of this mini-review.

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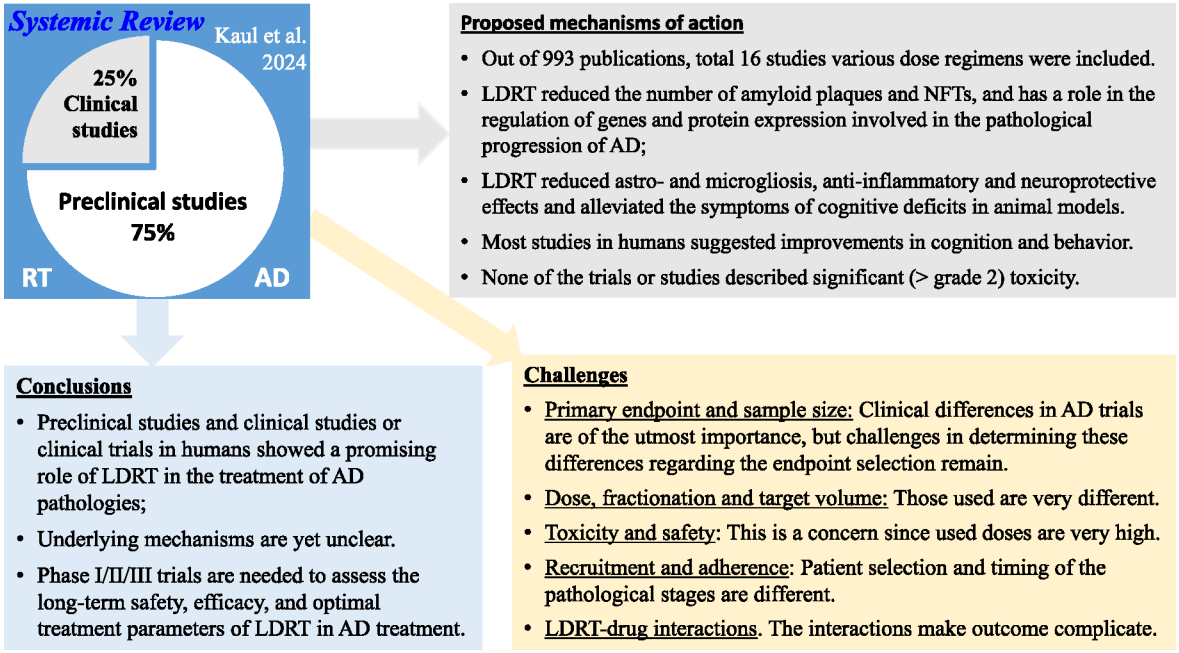

Fig. 1.

Summary of the Systemic Review on radiotherapy for human subjects and animal models of AD. The review was conducted based on 4 clinical studies and 12 preclinical studies with animal models (mice, rats and minipigs), which are representative of 25 % and 75 %, respectively, of the total 16 studies selected before July 1, 2023.[13] RT. Radiotherapy; AD. Alzheimer's Diseases.

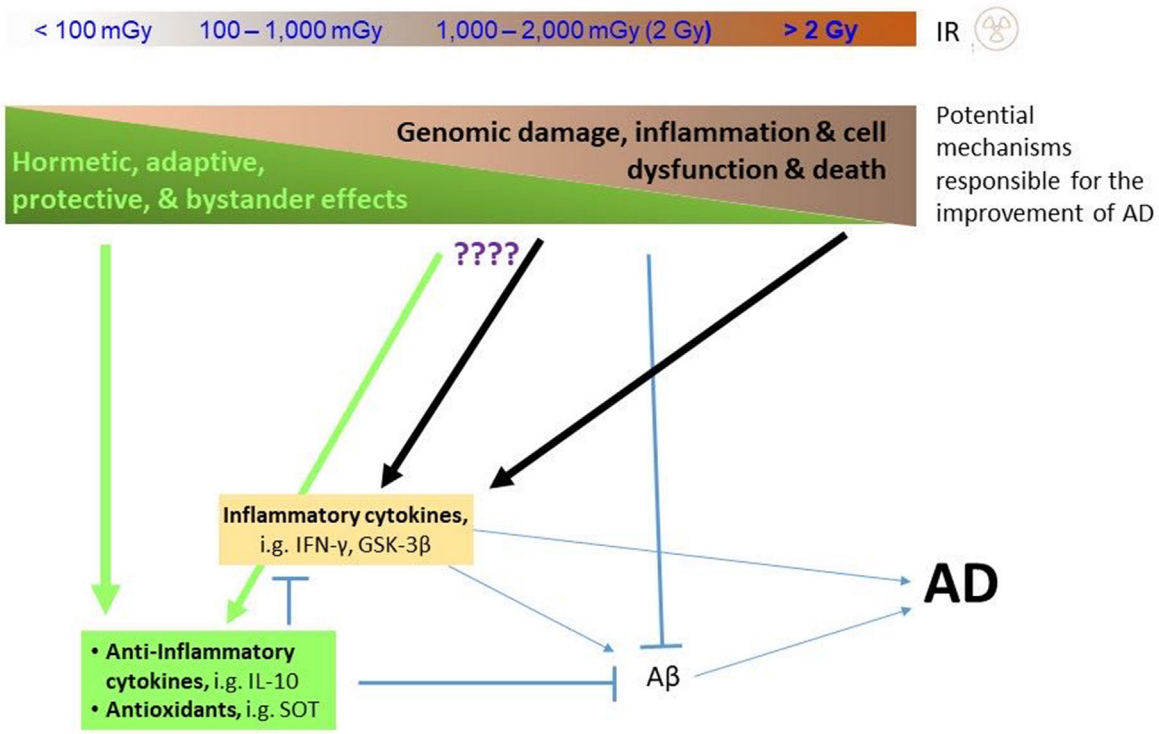

Fig. 2.

Illustrating different definitions of radiation doses and the potential biological effects for different dose ranges of radiation as well as the possible mechanisms by which LDRT induces pathways that in turn result in the preventive and therapeutic effects on the key pathogenesis and final outcomes of AD. IR. Ionizing radiation; SOD. superoxide dismutase.