

Does ionizing radiation influence Alzheimer's disease risk?

Nasrin BEGUM^{1,2}, Bing WANG², Masahiko MORI² and Guillaume VARES^{2,*}

¹Center for Nuclear Medicine and Ultrasound, Rajshahi Medical College Hospital Campus, GPO Box No. 35, Rajshahi, Bangladesh

²National Institute of Radiological Sciences, Anagawa 4-9-1, Inage-ku, Chiba 263-8555, Japan

*Corresponding author. Tel: +81-(0)43-206-4730; Email: vares@nirs.go.jp

(Received 12 March 2012; revised 22 May 2012; accepted 22 May 2012)

Alzheimer's disease (AD) is a human neurodegenerative disease, and its global prevalence is predicted to increase dramatically in the following decades. There is mounting evidence describing the effects of ionizing radiation (IR) on the brain, suggesting that exposure to IR might ultimately favor the development of AD. Therefore better understanding the possible connections between exposure to IR and AD pathogenesis is of utmost importance. In this review, recent developments in the research on the biological and cognitive effects of IR in the brain will be explored. Because AD is largely an age-related pathology, the effects of IR on ageing will be investigated.

Keywords: Alzheimer's disease; aging; dementia; cognitive effects; ionizing radiation

INTRODUCTION

Alzheimer's disease (AD) is the leading cause of dementia among the elderly and the fourth leading cause of death [1], with as many as 24 million affected people worldwide [2]. In the USA alone, it is estimated that 4.5 million people have AD [3], most of them older than 65 years old, with a prevalence of up to one-third of those aged more than 85 years [4]. Knowing that the global prevalence of AD is predicted to double every 20 years and reach 80 million by 2040 [2], it is absolutely crucial to better understand the various contributing factors and the molecular pathogenesis as part of an AD prevention strategy. Significant evidence suggests that exposure to ionizing radiation (IR) can lead to the development of AD. Although radiation therapy is an important tool in the treatment of primary [5] and metastatic [6] brain tumors, it is also responsible for various adverse neurological effects, such as cognitive dysfunction or dementia, which might occur in >20% of brain tumor patients aged 50 years or over and treated by radiotherapy [7, 8]. Recent work suggests that even relatively low dose exposures (such as those resulting from computed tomography (CT) scans) could trigger mechanisms associated with cognitive dysfunctions seen in normal aging and AD [9]. However, little is known regarding the molecular mechanisms involved in radiation-induced dementia. Therefore

understanding the biological effects of IR at low and high doses is emerging as a major neurological health concern.

ALZHEIMER'S DISEASE PATHOGENESIS AND GENETICS

AD is a progressive irreversible neurodegenerative disease, which accounts for 50–80% of all dementia cases [10–12]. The initiation of AD pathogenesis might start 10 years or more before the apparition of the first clinical symptoms [13].

AD is characterized by the accumulation of neuritic plaques and neurofibrillary tangles (NFT). The main component of the plaques is amyloid-beta (A β), a 4.5-kDa peptide resulting from the cleavage of amyloid precursor protein (APP). Ample evidence suggests that the accumulation of A β in the brain of AD patients, resulting from increased production or reduced clearance, is associated with inflammation [14], oxidative stress [15, 16], NFT formation [17], neuronal loss [18] and ultimately results in AD-related cognitive impairment [19].

The hypothesis that reactive oxygen species (ROS) formation resulted in neurodegeneration and plaque formation was formulated more than 20 years ago [20]. The correlation between ROS levels and degenerative diseases is now well established [21]. Brain cells of AD patients exhibit chronic

oxidative stress affecting not only the proteins of NFT and senile plaques, but also the cytoplasm of neuronal populations vulnerable to death during AD [22]. Elevated ROS levels result in damage to DNA, RNA, proteins and lipids [23]. Accumulating evidence suggests that oxidative RNA damage is a characteristic of vulnerable neurons at early stages of AD [24]; in a recent report, it was shown that neuronal RNA oxidation was higher in individuals showing mild cognitive impairment than in age-matched control individuals [25]. Increased levels of malondialdehyde (MDA), a ketoaldehyde produced by peroxidative decomposition of unsaturated lipids, were observed in the brains of AD patients [26]. In support for the major role of oxidative stress in AD, the administration of anti-oxidant vitamins and products reduced AD incidence in patients [27].

A number of studies pinpoint mitochondrial dysfunction as a leading cause of oxidative stress in AD [28–30]. In earlier stages of AD pathogenesis, oxidative stress might result in A β deposition in order to shield neurons from oxidative damage [31]. Subsequently, accumulated A β causes Ca²⁺-dependent oxidative stress by stimulating NADPH oxidase in astrocytes, leading to depleted glutathione (GSH) levels in astrocytes and nearby neurons, which might be sufficient to cause neuronal death [32]. A β accumulation leads to increased ROS levels, which target mitochondrial enzymes such as α -ketoglutarate dehydrogenase and aconitase, resulting in impaired mitochondrial function and ultimately further increases in ROS levels [1]. Decreased cytochrome c oxidase (COX) activity was observed in the brains of patients with AD [33] and was associated with deficits in cognitive abilities [34].

Recent genome-wide association studies (GWAS) have associated several genetic factors (*ABCA7*, *APOE*, *BINI*, *CD2AP*, *CD33*, *CLU*, *CRI*, *MS4A4E*, *MS4A6A* and *PICALM*) with increased risk for late-onset sporadic AD [2, 35–38]. The only firmly established genetic variant for AD is the 4 allele of the Apolipoprotein E gene (*APOE-4*) on chromosome 19 [35]. Individuals with two copies of the *APOE-4* allele have a 50–90% probability of developing AD by the age of 85, and those with one copy are still three times more likely to develop AD than individuals expressing other variants [39]. Recently, molecular pathway analyses on several GWAS datasets suggest that immune response and sterol and lipid metabolism could be associated with the etiology of AD [40].

EFFECTS OF IONIZING RADIATION ON THE BRAIN

Physiological and cognitive effects

The brain is generally considered to be relatively resistant to IR because neurons are resistant to radiation-induced cell killing [41]. However, a number of studies have described the existence of various physiological and cognitive effects

of IR at various doses [41, 42]. While macroscopic changes (radiation myelopathy) are easily observable only after high dose medical exposures (above 60 Gy in conventional fractionation) [43], lower doses can nonetheless lead to cognitive dysfunction without inducing significant morphological change [43].

Such cognitive changes are often manifested as deficits in hippocampal-dependent functions of learning, memory and spatial information processing [44–46]. Some reports have suggested that cognitive dysfunction, including dementia, can be observed in 20–50% of long-term brain tumor survivors older than 50 years treated by radiotherapy [7, 8, 47]. CT and magnetic resonance imaging (MRI) data have shown evidence of progressive brain atrophy [48] or global damage of the cerebral white matter [7]. The neurological deficits of high-dose radiation are progressively detrimental over time and are thought to be due to demyelination and neural loss with associated neural and cognitive deficiencies. Some of these cognitive defects have been observed as a consequence of impaired neurogenesis after exposure to IR [49].

Actively dividing cells are known to be more sensitive to IR than cells having completed division or differentiated cells that seldom undergo division. Radiation effects in the central nervous system (CNS) are more pronounced in children than in adults; IR-induced cognitive effects include learning disabilities and are more pronounced in children younger than 4–7 years old [42]. Mental retardation resulting from prenatal irradiation in Hiroshima and Nagasaki is also well documented and the critical time of exposure is between the 8th and the 15th week of gestation, coinciding with a window of neuronal cell migration in the developing brain [50].

Ionizing radiation induces vascular abnormalities, demyelination and alterations in the microenvironment of the brain, shifting the proliferative response of progenitors from neurogenesis to gliogenesis [51]. Twenty-one-day-old mice exposed to 2–10 Gy X-rays exhibited persistent changes in neurogenesis, which were associated with spatial memory retention deficits at 3 months post treatment [52]. A single dose of 1–15 Gy to the heads of adult mice or rats permanently abolished adult neurogenesis in the dentate gyrus without incapacitating the animals [53]. In contrast, a recent study using a single dose of 4 Gy to young adult mice found a reversible effect on proliferation and neurogenesis in the dentate gyrus [54]. Ischemic brain injury increases neurogenesis in rodent brains [55, 56]. Newborn neurons can become functionally integrated into the dentate gyrus [57]. Importantly, newly generated neurons may play a significant role in synaptic plasticity, and a reduction in the number of these cells or the inhibition of neurogenesis impairs spatial learning and causes cognitive deficiencies [52, 58, 59]. It was recently shown that 8 Gy irradiation of 10-day-old mice resulted in decreased hippocampal

neurogenesis and subsequently increased the susceptibility of the adult brain to hypoxia-ischemia [60].

Other IR effects on the CNS include acute disruption of the blood–brain barrier (BBB), resulting from radiation-induced apoptosis of microvascular endothelial cells, as observed in mice and rats exposed to 50-Gy X-rays [61]. In rats irradiated with 5–200 Gy X-rays, 15% of the endothelial cells in the brain were lost within 24 h of irradiation [62]. Using acid sphingomyelinase (ASMase) knockout mice, several studies have shown that IR-induced endothelial apoptosis is mediated by the ASMase pathway [61, 63].

Cerebral microvascular pathology precedes and accompanies age-related cognitive dysfunction and neurodegeneration [64]. Acute vascular changes within 24 h after irradiation include increased vascular endothelial cell swelling, vascular permeability and edema, lymphocyte adhesion and infiltration and apoptosis. Late vascular effects occur weeks to months after irradiation, and include capillary collapse, thickening of basement membrane, scarring and fibrosis, teleangiectasis and loss of clonogenic capacity [63].

Molecular effects

ATM- and p53-dependent radiation-induced apoptosis was observed in several parts of the brain [65], relying on BAX-mediated activation of caspase 3 [66]. IR also induced increased expression of pro-inflammatory cytokines, such as Tumor necrosis factor- α (TNF- α) and Interferon- γ (IFN- γ) [41, 67, 68], or adhesion molecules like E-selectin and Intercellular Adhesion Molecule 1 (ICAM-1) [69].

There is no shortage of studies describing gene modulations resulting from exposure to IR at various doses in a number of experimental models [70–73], including in the brain [9, 49, 74]. A recent study has shown that exposure to low doses of IR trigger gene modulations that are different from those triggered by high doses and involve genes associated with damage response functions (such as those controlled by Trp53 and Myc) and brain-specific functions, such as memory, learning and cognition [9]. Overall, early IR-induced changes involved signal transduction mechanisms, ion regulation and synaptic signaling; late changes involved metabolic functions, including myelin and protein synthesis [74]. Low dose IR also modulated the expression of genes involved in stress response, cell cycle control and DNA synthesis/repair [74].

RADIATION AND AGEING

The relationship between IR and ageing has been thoroughly investigated for several decades [75]. IR has been associated with various age-related effects, such as cardiovascular diseases [76, 77], cataracts [78], osteoporosis [79], digestive and respiratory diseases [77]. Exposure to IR shortened the life span of radiologists, radium dial

painters, Thorotrast patients and atomic bomb survivors [80, 81]. IR-induced oxidative damage is acknowledged to contribute to ageing in the brain and other organs [82]. Indeed, elevated ROS levels and oxidative DNA damage (such as 8-hydroxydeoxyguanosine-8-oxo-dG) were associated with decreased levels of glutathione peroxidase Cu/Zn superoxide dismutase (SOD), catalase (in the cytosol and cell nucleus) and the manganese form of SOD (Mn-SOD, in mitochondria) in ageing human skin fibroblasts [83]. There has been mounting evidence that antioxidant activity declines with age, resulting in elevated oxidative damage to lipids, proteins and DNA [84–86].

During the past 20 years, a number of studies have shown that the progressive loss of telomeres plays a major part in the aging process of somatic cells [87–89], by ultimately triggering DNA damage signals [90, 91] and senescence. It was noticed that the G-rich nature of telomeric DNA makes it sensitive to oxidative damage [92]. In human cells, IR induced c-Abl-dependent phosphorylation of the telomerase protein (hTERT), which resulted in the inhibition of hTERT activity and a decrease in telomere length [93]. Irradiated mouse fetuses with forelimb defects exhibited shortened telomeres [94].

IS IONIZING RADIATION A RISK FACTOR FOR AD?

Altogether, the above-mentioned available data indicate that low and high doses of IR trigger molecular mechanisms that could ultimately result in cognitive dysfunction, suggesting that IR might be a risk factor for the induction of AD.

The question of whether AD onset or prevalence might be influenced by IR is of particular interest in the context of low dose medical irradiations or for space research studies.

The Linear Non-Threshold (LNT) model is currently applied to estimate the health risks from low doses of IR [95] but there is strong controversy as to whether biological effects of radiation are really linear with dose or whether there is a threshold below which no biological effect could be observed. Slight AD risk resulting from non-IR exposure (such as extremely low frequency electromagnetic fields – ELF-EMF) has been described [96]. Non-cancer risks resulting from low dose IR exposures have been observed, for example in Japanese atomic bomb survivors [97], but these included no significant increase in AD prevalence or mortality [77, 98]. To date, there is no epidemiological data linking low dose IR exposure with increased AD. Large-scale population studies are urgently needed to measure the risks resulting from IR exposure in terms of AD induction.

In agreement with the idea that low-dose IR is a potential risk factor for AD, Lowe *et al.* have shown that the global

gene modulations in the brain of irradiated mice were similar to those observed in aged individuals or in AD patients [9]. Gamma-irradiation of B6C3F1 mice triggered the expression of the troponin T1 gene (*TNNT1*), an early biomarker of CNS stress [49].

Long-term exposure to radiation represents a significant risk factor during space travel missions. Astronauts are exposed to high-LET radiation from galactic cosmic rays with potential deleterious consequences for the CNS. A certain amount of interest has been given to the potential risks (including AD risks) associated with space travel. A recent report has shown that exposure to high energy $^{56}\text{Fe}^{26+}$ iron nuclei accelerated age-related neurological dysfunction in APP23 transgenic mice overexpressing human APP [99]. Knowing that AD was often described as a process similar to accelerated ageing [100], the authors concluded that exposure to cosmic high-energy particles might accelerate AD-related neurological deficits.

Further studying the effects of IR on ageing could provide new evidence linking IR and AD. IR, ageing and AD are all associated with elevated oxidative damage levels [15, 26, 82–84]. Telomere shortening is one of the ageing-related mechanisms potentially involved in AD, as it might cause the accumulation of DNA damage and sensitize neurons to oxidative stress [101]. Furthermore, it has been shown that oxidative stress can itself trigger telomere shortening [102]. Telomere shortening was accelerated in lymphocytes of AD patients [103–105], but it was not observed in neurons [105]. The presence of shorter telomeres was associated with increased mortality in individuals carrying the *APOE-4* allele or with AD [104]. In the human brain, neurogenesis occurs in the dentate gyrus, and it has been suggested that the combination of telomere shortening and decreased neurogenesis might predispose to AD [106]. A recent investigation however showed that telomere shortening slowed down the progression of amyloid plaques in APP transgenic mice [107].

Epidemiological studies have identified risk factors for AD, such as hypertension, hypercholesterolemia, diabetes and air pollution [108–111]. Interestingly, cardiovascular diseases are also among documented aging-related non-cancer effects of IR [76, 77], as mentioned above. Exposure to air pollution can lead to chronic oxidative stress through the production of inflammatory cytokines [112], accelerated amyloid- β accumulation and AD-like brain pathology [113]. Furthermore, there is increasing evidence that oxidative stress (resulting for example from IR exposure) is strongly involved in the pathogenesis of diabetes through the inhibition of insulin expression and increased apoptosis [114]. These data bring additional weight to the idea that AD and IR effects are somehow linked.

Finally, developing discoveries of the genetic factors associated with AD [115] might bring some understanding

of the possible connections between IR and AD. For example, it has been shown by GWAS that a variant for the locus containing the clusterin gene (*CLU*, or apolipoprotein J; *APOJ*) is associated with susceptibility for late-onset AD [38]. Clusterin gene expression is responsive to various stress-inducing agents, including IR [116] and oxidative stress [117]; it has been involved in ageing and various ageing-related pathological conditions like atherosclerosis, kidney degenerative diseases and neurodegenerative diseases (AD, Scrapie, Pick's disease) [118, 119]. Membrane-spanning-4-domains, subfamily A, member 6A (*MS4A6A*) is another locus associated with AD by GWAS [36]. *MS4A6A* expression was modulated in human lymphocytes exposed to α particles [40], but additional data are needed to determine the relevance of *MS4A6A* in the CNS and after other medically relevant sources of IR.

Future investigations will probably identify new genetic factors and rare variants (occurring in less than 1% of the population) for AD and ageing, which might in combination with IR influence AD risk in sensitive subgroups of the population.

Recent advances in neuroimaging and other bioassays bring new opportunities to detect AD at an early preclinical stage. For example, high position emission tomography (PET) amyloid tracer retention and low levels of amyloid- β levels in the cerebrospinal fluid (CSF) might constitute markers of the first stage of preclinical AD (or asymptomatic cerebral amyloidosis) [120]. In the future, a proactive AD prevention strategy might include early screening of individuals at risk of developing AD based on risk and genetic factors as well as irradiation history.

CONCLUSION

In the absence of conclusive epidemiological or molecular data proving unequivocally that exposure to IR increases the risk of developing AD, the precise relationship between IR and AD pathogenesis cannot be drawn. However, given the strong association between AD and ageing, and in light of the studies describing the general effects of IR on ageing, there is consistent evidence that IR might trigger mechanisms that could ultimately favor AD. Elevated oxidative damage has been seen both in the context of normal ageing and during AD pathogenesis, and it can be triggered by IR exposure. There are strong arguments for a major involvement of oxidative stress in AD pathogenesis, suggesting that agents modulating oxidative stress (such as IR) might directly influence the development of AD. Additional investigations about IR-induced aging might give us new clues concerning the possible effects in terms of AD, in particular in conjunction with other AD risk factors. Finally, a better understanding of the possible interactions between AD genetic factors (such as *APOE-4* or *CLU*) and IR is necessary.

ACKNOWLEDGEMENTS

Dr Nasrin Begum was a fellow of the Nuclear Researchers Exchange Programme 2011 supported by the Ministry of Education, Culture, Sport, Sciences and Technology (MEXT) and the Nuclear Safety Research Association of Japan. The authors would like to thank Ms Kourtney Richardson for proofreading the manuscript.

REFERENCES

- Wang X, Su B, Perry G *et al.* Insights into amyloid-beta-induced mitochondrial dysfunction in Alzheimer disease. *Free Radic Biol Med* 2007;**43**:1569–73.
- Hampel H, Prvulovic D, Teipel S *et al.* The future of Alzheimer's disease: the next 10 years. *Prog Neurobiol* 2011;**95**:718–28.
- Hebert LE, Scherr PA, Bienias JL *et al.* Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Arch Neurol* 2003;**60**:1119–22.
- Philipson O, Lord A, Gumucio A *et al.* Animal models of amyloid-beta-related pathologies in Alzheimer's disease. *FEBS J* 2010;**277**:1389–409.
- Chandana SR, Movva S, Arora M *et al.* Primary brain tumors in adults. *Am Fam Physician* 2008;**77**:1423–30.
- Elaimy AL, Mackay AR, Lamoreaux WT *et al.* Clinical outcomes of stereotactic radiosurgery in the treatment of patients with metastatic brain tumors. *World Neurosurg* 2011;**75**:673–83.
- Asai A, Matsutani M, Kohno T *et al.* Subacute brain atrophy after radiation therapy for malignant brain tumor. *Cancer* 1989;**63**:1962–74.
- Imperato JP, Paleologos NA, Vick NA. Effects of treatment on long-term survivors with malignant astrocytomas. *Ann Neurol* 1990;**28**:818–22.
- Lowe XR, Bhattacharya S, Marchetti F *et al.* Early brain response to low-dose radiation exposure involves molecular networks and pathways associated with cognitive functions, advanced aging and Alzheimer's disease. *Radiat Res* 2009;**171**:53–65.
- Cacabelos R. Pharmacogenomics and therapeutic prospects in dementia. *Eur Arch Psychiatry Clin Neurosci* 2008;**258** (Suppl 1):28–47.
- Demarin V, Zavoreo I, Kes VB *et al.* Biomarkers in Alzheimer's disease. *Clin Chem Lab Med* 2011;**49**:773–8.
- Schaeffer EL, Figueiro M, Gattaz WF. Insights into Alzheimer disease pathogenesis from studies in transgenic animal models. *Clinics (Sao Paulo)* 2011;**66**(Suppl 1):45–54.
- Sperling RA, Aisen PS, Beckett LA *et al.* Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;**7**:280–92.
- Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease —a brief review of the basic science and clinical literature. *Cold Spring Harb Perspect Med* 2012;**2**:a006346.
- Nunomura A, Perry G, Aliev G *et al.* Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol* 2001;**60**:759–67.
- Smith MA, Hirai K, Hsiao K *et al.* Amyloid-beta deposition in Alzheimer transgenic mice is associated with oxidative stress. *J Neurochem* 1998;**70**:2212–15.
- Jucker M, Walker LC. Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. *Ann Neurol* 2011;**70**:532–40.
- Calissano P, Matrone C, Amadoro G. Apoptosis and in vitro Alzheimer disease neuronal models. *Commun Integr Biol* 2009;**2**:163–9.
- Patrias LM, Klaver AC, Coffey MP *et al.* Effects of external beam radiation on in vitro formation of Abeta1–42 fibrils and preformed fibrils. *Radiat Res* 2011;**175**:375–81.
- Frautschy SA, Baird A, Cole GM. Effects of injected Alzheimer beta-amyloid cores in rat brain. *Proc Natl Acad Sci USA* 1991;**88**:8362–6.
- Valko M, Leibfritz D, Moncol J *et al.* Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 2007;**39**:44–84.
- Hirai K, Aliev G, Nunomura A *et al.* Mitochondrial abnormalities in Alzheimer's disease. *J Neurosci* 2001;**21**:3017–23.
- Markesbery WR, Lovell MA. Damage to lipids, proteins, DNA, and RNA in mild cognitive impairment. *Arch Neurol* 2007;**64**:954–6.
- Nunomura A, Hofer T, Moreira PI *et al.* RNA oxidation in Alzheimer disease and related neurodegenerative disorders. *Acta Neuropathol* 2009;**118**:151–66.
- Nunomura A, Perry G, Aliev G *et al.* Oxidative damage is the earliest event in Alzheimer disease. *J Neuropathol Exp Neurol* 2001;**60**:759–67.
- Dalle-Donne I, Rossi R, Colombo R *et al.* Biomarkers of oxidative damage in human disease. *Clin Chem* 2006;**52**:601–23.
- Mancuso C, Bates TE, Butterfield DA *et al.* Natural antioxidants in Alzheimer's disease. *Expert Opin Investig Drugs* 2007;**16**:1921–31.
- Beal MF. Mitochondrial dysfunction in neurodegenerative diseases. *Biochim Biophys Acta* 1998;**1366**:211–23.
- Manczak M, Park BS, Jung Y *et al.* Differential expression of oxidative phosphorylation genes in patients with Alzheimer's disease: implications for early mitochondrial dysfunction and oxidative damage. *Neuromolecular Med* 2004;**5**:147–62.
- Reddy PH and Beal MF. Are mitochondria critical in the pathogenesis of Alzheimer's disease? *Brain Res Brain Res Rev* 2005;**49**:618–32.
- Varadarajan S, Yatin S, Aksenova M *et al.* Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. *J Struct Biol* 2000;**130**:184–208.
- Abramov AY, Canevari L, Duchen MR. Calcium signals induced by amyloid beta peptide and their consequences in neurons and astrocytes in culture. *Biochim Biophys Acta* 2004;**1742**:81–7.
- Maurer I, Zierz S, Möller HJ. A selective defect of cytochrome c oxidase is present in brain of Alzheimer disease patients. *Neurobiol Aging* 2000;**21**:455–62.

34. Berndt JD, Callaway NL, Gonzalez-Lima F. Effects of chronic sodium azide on brain and muscle cytochrome oxidase activity: a potential model to investigate environmental contributions to neurodegenerative diseases. *J Toxicol Environ Health A* 2001;**63**:67–77.
35. Bertram L, McQueen MB, Mullin K *et al.* Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet* 2007;**39**:17–23.
36. Hollingworth P, Harold D, Sims R *et al.* Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. *Nat Genet* 2011;**43**:429–35.
37. Naj AC, Jun G, Beecham GW *et al.* Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. *Nat Genet* 2011;**43**:436–41.
38. Lambert J-C, Heath S, Even G *et al.* Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* 2009;**41**:1094–99.
39. Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat Rev Neurosci* 2009;**10**:333–44.
40. Jones L, Holmans PA, Hamshe ML *et al.* Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer's disease. *PLoS One* 2010;**5**:e13950.
41. Belka C, Budach W, Kortmann RD *et al.* Radiation induced CNS toxicity—molecular and cellular mechanisms. *Br J Cancer* 2001;**85**:1233–9.
42. Schultheiss TE, Kun LE, Ang KK *et al.* Radiation response of the central nervous system. *Int J Radiat Oncol Biol Phys* 1995;**31**:1093–112.
43. Abayomi OK. Pathogenesis of irradiation-induced cognitive dysfunction. *Acta Oncol* 1996;**35**:659–63.
44. Mizumatsu S, Monje ML, Morhardt DR *et al.* Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res* 2003;**63**:4021–7.
45. Raber J. Unintended effects of cranial irradiation on cognitive function. *Toxicol Pathol* 2010;**38**:198–202.
46. Raber J, Villasana L, Rosenberg J *et al.* Irradiation enhances hippocampus-dependent cognition in mice deficient in extracellular superoxide dismutase. *Hippocampus* 2011;**21**:72–80.
47. Maire JP, Coudin B, Guérin J *et al.* Neuropsychologic impairment in adults with brain tumors. *Am J Clin Oncol* 1987;**10**:156–62.
48. Suzuki Y, Tanaka R, Miyakawa T *et al.* Evaluation of radiation therapy for metastatic brain tumor by computed tomography. *Neurol Med Chir (Tokyo)* 1985;**25**:837–43.
49. Lowe XR, Marchetti F, Lu X *et al.* Molecular stress response in the CNS of mice after systemic exposure to interferon-alpha, ionizing radiation and ketamine. *Neurotoxicology* 2009;**30**:261–8.
50. Schull WJ, Otake M. Cognitive function and prenatal exposure to ionizing radiation. *Teratology* 1999;**59**:222–6.
51. Monje ML, Mizumatsu S, Fike JR *et al.* Irradiation induces neural precursor-cell dysfunction. *Nat Med* 2002;**8**:955–62.
52. Rola R, Raber J, Rizk A *et al.* Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. *Exp Neurol* 2004;**188**:316–30.
53. Monje ML, Toda H, Palmer TD. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 2003;**302**:1760–5.
54. Ben Abdallah NM-B, Slomianka L, Lipp H-P. Reversible effect of X-irradiation on proliferation, neurogenesis, and cell death in the dentate gyrus of adult mice. *Hippocampus* 2007;**17**:1230–40.
55. Arvidsson A, Kokaia Z, Airaksinen MS *et al.* Stroke induces widespread changes of gene expression for glial cell line-derived neurotrophic factor family receptors in the adult rat brain. *Neuroscience* 2001;**106**:27–41.
56. Liu J, Solway K, Messing RO *et al.* Increased neurogenesis in the dentate gyrus after transient global ischemia in gerbils. *J Neurosci* 1998;**18**:7768–78.
57. van Praag H, Schinder AF, Christie BR *et al.* Functional neurogenesis in the adult hippocampus. *Nature* 2002;**415**:1030–4.
58. Raber J, Rola R, LeFevour A *et al.* Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res* 2004;**162**:39–47.
59. Shors TJ, Townsend DA, Zhao M *et al.* Neurogenesis may relate to some but not all types of hippocampal-dependent learning. *Hippocampus* 2002;**12**:578–84.
60. Zhu C, Huang Z, Gao J *et al.* Irradiation to the immature brain attenuates neurogenesis and exacerbates subsequent hypoxic-ischemic brain injury in the adult. *J Neurochem* 2009;**111**:1447–56.
61. Li Y-Q, Chen P, Haimovitz-Friedman A *et al.* Endothelial apoptosis initiates acute blood-brain barrier disruption after ionizing radiation. *Cancer Res* 2003;**63**:5950–6.
62. Ljubimova NV, Levitman MK, Plotnikova ED *et al.* Endothelial cell population dynamics in rat brain after local irradiation. *Br J Radiol* 1991;**64**:934–40.
63. Peña LA, Fuks Z, Kolesnick RN. Radiation-induced apoptosis of endothelial cells in the murine central nervous system: protection by fibroblast growth factor and sphingomyelinase deficiency. *Cancer Res* 2000;**60**:321–7.
64. Brown WR, Thore CR. Review: cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol Appl Neurobiol* 2011;**37**:56–74.
65. Herzog KH, Chong MJ, Kapsetaki M *et al.* Requirement for Atm in ionizing radiation-induced cell death in the developing central nervous system. *Science* 1998;**280**:1089–91.
66. Chong MJ, Murray MR, Gosink EC *et al.* Atm and Bax cooperate in ionizing radiation-induced apoptosis in the central nervous system. *Proc Natl Acad Sci USA* 2000;**97**:889–94.
67. Hallahan DE, Spriggs DR, Beckett MA *et al.* Increased tumor necrosis factor alpha mRNA after cellular exposure to ionizing radiation. *Proc Natl Acad Sci USA* 1989;**86**:10104–7.
68. Cammer W. Effects of TNF α on immature and mature oligodendrocytes and their progenitors in vitro. *Brain Res* 2000;**864**:213–19.

69. Quarmby S, Kumar P, Kumar S. Radiation-induced normal tissue injury: role of adhesion molecules in leukocyte–endothelial cell interactions. *Int J Cancer* 1999;**82**:385–95.
70. Amundson SA. Functional genomics in radiation biology: a gateway to cellular systems-level studies. *Radiat Environ Biophys* 2008;**47**:25–31.
71. Kalanxhi E, Dahle J. Genome-wide microarray analysis of human fibroblasts in response to γ radiation and the radiation-induced bystander effect. *Radiat Res* 2012;**177**:35–43.
72. Roy L, Gruel G, Vaurijoux A. Cell response to ionising radiation analysed by gene expression patterns. *Ann Ist Super Sanita* 2009;**45**:272–7.
73. Vares G, Wang B, Shang Y *et al.* Adaptive response in embryogenesis: vi. Comparative microarray analysis of gene expressions in mouse fetuses. *Int J Radiat Biol* 2009;**85**:70–86.
74. Yin E, Nelson DO, Coleman MA *et al.* Gene expression changes in mouse brain after exposure to low-dose ionizing radiation. *Int J Radiat Biol* 2003;**79**:759–75.
75. Richardson RB. Ionizing radiation and aging: rejuvenating an old idea. *Aging (Albany NY)* 2009;**1**:887–902.
76. Cardis E, Gilbert ES, Carpenter L *et al.* Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res* 1995;**142**:117–32.
77. Preston DL, Shimizu Y, Pierce DA *et al.* Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. *Radiat Res* 2003;**160**:381–407.
78. Neriishi K, Nakashima E, Minamoto A *et al.* Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold. *Radiat Res* 2007;**168**:404–8.
79. Hamilton SA, Pecaunt MJ, Gridley DS *et al.* A murine model for bone loss from therapeutic and space-relevant sources of radiation. *J Appl Physiol* 2006;**101**:789–93.
80. Anderson RE. Longevity in radiated human populations, with particular reference to the atomic bomb survivors. *Am J Med* 1973;**55**:643–56.
81. Becker N, Liebermann D, Wesch H *et al.* Mortality among Thorotrast-exposed patients and an unexposed comparison group in the German Thorotrast study. *Eur J Cancer* 2008;**44**:1259–68.
82. Floyd RA. Antioxidants, oxidative stress, and degenerative neurological disorders. *Proc Soc Exp Biol Med* 1999;**222**:236–45.
83. Lu CY, Lee HC, Fahn HJ *et al.* Oxidative damage elicited by imbalance of free radical scavenging enzymes is associated with large-scale mtDNA deletions in aging human skin. *Mutat Res* 1999;**423**:11–21.
84. Mecocci P, Fanó G, Fulle S *et al.* Age-dependent increases in oxidative damage to DNA, lipids, and proteins in human skeletal muscle. *Free Radic Biol Med* 1999;**26**:303–8.
85. Mutlu-Türkolu U, İlhan E, Oztezcan S *et al.* Age-related increases in plasma malondialdehyde and protein carbonyl levels and lymphocyte DNA damage in elderly subjects. *Clin Biochem* 2003;**36**:397–400.
86. Stadtman ER. Protein oxidation and aging. *Free Radic Res* 2006;**40**:1250–8.
87. Harley CB, Futcher AB, Greider CW. Telomeres shorten during ageing of human fibroblasts. *Nature* 1990;**345**:458–60.
88. Hastie ND, Dempster M, Dunlop MG *et al.* Telomere reduction in human colorectal carcinoma and with ageing. *Nature* 1990;**346**:866–8.
89. Lindsey J, McGill NI, Lindsey LA *et al.* In vivo loss of telomeric repeats with age in humans. *Mutat Res* 1991;**256**:45–8.
90. d'Adda di Fagagna F, Reaper PM, Clay-Farrace L *et al.* A DNA damage checkpoint response in telomere-initiated senescence. *Nature* 2003;**426**:194–8.
91. Takai H, Smogorzewska A, de Lange T. DNA damage foci at dysfunctional telomeres. *Curr Biol* 2003;**13**:1549–56.
92. Henle ES, Han Z, Tang N *et al.* Sequence-specific DNA cleavage by Fe²⁺-mediated fenton reactions has possible biological implications. *J Biol Chem* 1999;**274**:962–71.
93. Kharbanda S, Kumar V, Dhar S *et al.* Regulation of the hTERT telomerase catalytic subunit by the c-Abl tyrosine kinase. *Curr Biol* 2000;**10**:568–75.
94. Derradji H, Bekaert S, De Meyer T *et al.* Ionizing radiation-induced gene modulations, cytokine content changes and telomere shortening in mouse fetuses exhibiting forelimb defects. *Dev Biol* 2008;**322**:302–13.
95. Little MP. Do non-targeted effects increase or decrease low dose risk in relation to the linear-non-threshold (LNT) model? *Mutat Res* 2010;**687**:17–27.
96. García AM, Sisternas A, Hoyos SP. Occupational exposure to extremely low frequency electric and magnetic fields and Alzheimer disease: a meta-analysis. *Int J Epidemiol* 2008;**37**:329–40.
97. Little MP. Cancer and non-cancer effects in Japanese atomic bomb survivors. *J Radiol Prot* 2009;**29**:A43–A59.
98. Yamada M, Sasaki H, Mimori Y *et al.* Prevalence and risks of dementia in the Japanese population: RERF's adult health study Hiroshima subjects. Radiation Effects Research Foundation. *J Am Geriatr Soc* 1999;**47**:189–95.
99. Vlkolinsky R, Titova E, Krucker T *et al.* Exposure to ⁵⁶Fe-particle radiation accelerates electrophysiological alterations in the hippocampus of APP23 transgenic mice. *Radiat Res* 2010;**173**:342–52.
100. Waldau B, Shetty AK. Behavior of neural stem cells in the Alzheimer brain. *Cell Mol Life Sci* 2008;**65**:2372–84.
101. Zhang P, Dilley C, Mattson MP. DNA damage responses in neural cells: focus on the telomere. *Neuroscience* 2007;**145**:1439–48.
102. von Zglinicki T, Saretzki G, Döcke W *et al.* Mild hyperoxia shortens telomeres and inhibits proliferation of fibroblasts: a model for senescence? *Exp Cell Res* 1995;**220**:186–93.
103. Zhang J, Kong Q, Zhang Z *et al.* Telomere dysfunction of lymphocytes in patients with Alzheimer disease. *Cogn Behav Neurol* 2003;**16**:170–6.
104. Honig LS, Schupf N, Lee JH *et al.* Shorter telomeres are associated with mortality in those with APOE 4 and dementia. *Ann Neurol* 2006;**60**:181–7.

105. Panossian LA, Porter VR, Valenzuela HF *et al.* Telomere shortening in T cells correlates with Alzheimer's disease status. *Neurobiol Aging* 2003;**24**:77–84.
106. Ming G-L, Song H. Adult neurogenesis in the mammalian central nervous system. *Annu Rev Neurosci* 2005;**28**:223–50.
107. Rolyan H, Scheffold A, Heinrich A *et al.* Telomere shortening reduces Alzheimer's disease amyloid pathology in mice. *Brain* 2011;**134**:2044–56.
108. Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch Neurol* 2009;**66**:300–5.
109. Arvanitakis Z, Wilson RS, Bienias JL *et al.* Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol* 2004;**61**:661–6.
110. Yaffe K, Fiocco AJ, Lindquist K *et al.* Predictors of maintaining cognitive function in older adults: the Health ABC study. *Neurology* 2009;**72**:2029–35.
111. Moulton PV, Yang W. Air pollution, oxidative stress, and Alzheimer's disease. *J Environ Public Health* 2012;**2012**:472751.
112. Delfino RJ, Staimer N, Vaziri ND. Air pollution and circulating biomarkers of oxidative stress. *Air Quality, Atmosphere & Health* 2011;**4**:37–52.
113. Calderón-Garcidueñas L, Kavanaugh M, Block M *et al.* Neuroinflammation, hyperphosphorylated tau, diffuse amyloid plaques, and down-regulation of the cellular prion protein in air pollution exposed children and young adults. *J Alzheimers Dis* 2012;**28**:93–107.
114. Yang H, Jin X, Kei Lam CW *et al.* Oxidative stress and diabetes mellitus. *Clin Chem Lab Med* 2011;**49**:1773–82.
115. Hampel H, Prvulovic D, Teipel S *et al.* The future of Alzheimer's disease: the next 10 years. *Prog Neurobiol* 2011;**95**:718–28.
116. Klokov D, Criswell T, Leskov KS *et al.* IR-inducible clusterin gene expression: a protein with potential roles in ionizing radiation-induced adaptive responses, genomic instability, and bystander effects. *Mutat Res* 2004;**568**:97–110.
117. Trougakos IP, Gonos ES. Regulation of clusterin/apolipoprotein J, a functional homologue to the small heat shock proteins, by oxidative stress in ageing and age-related diseases. *Free Radic Res* 2006;**40**:1324–34.
118. Rosenberg ME, Silkensen J. Clusterin: physiologic and pathophysiologic considerations. *Int J Biochem Cell Biol* 1995;**27**:633–45.
119. Calero M, Rostagno A, Matsubara E *et al.* Apolipoprotein (J clusterin) and Alzheimer's disease. *Microsc Res Tech* 2000;**50**:305–15.
120. Sperling RA, Aisen PS, Beckett LA *et al.* Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;**7**:280–92.