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Aging attenuates radiation-induced expression of pro-inflammatory mediators in rat brain

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Abstract

The present study was designed to examine the effect of aging on radiation-induced expression of pro-inflammatory mediators in rat brain. Male F344×BN rats (4, 16, and 24 months of age) received either whole brain irradiation with a single dose of 10Gy γ -rays or sham-irradiation, and were maintained for 4, 8, and 24 h post-irradiation. The mRNA expression levels of various pro-inflammatory mediators such as cytokines, adhesion molecules, chemokine, and matrix metalloproteinase were analyzed by quantitative real-time reverse transcription-polymerase chain reaction (RT-PCR). The acute inflammatory responses to irradiation, including overexpression of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin, monocyte chemoattractant protein-1 (MCP-1), and matrix metalloproteinase-9 (MMP-9) were markedly attenuated in the hippocampus of middle-aged and old rats compared with young groups. Specifically, a significant age-dependent decrease in TNF- α expression was detected 8 and 24 h after irradiation and a similar age-related attenuation was observed in IL-1 β , ICAM-1, and VCAM-1 expression 4 and 8 h post-irradiation. MCP-1 expression was reduced 4 h post-irradiation and MMP-9 expression at 8 h post-irradiation. These results provide evidence for the first time that radiation-induced pro-inflammatory responses in the brain are suppressed in aged animals.

Keywords

Aging; Pro-inflammatory mediators; Brain inflammation; Whole brain irradiation

It is well documented that an impaired immune response is associated with aging. Gon et al. [10] demonstrated that the serum concentrations of pro-inflammatory cytokines including TNF- α and IL-1 β were significantly lower in elderly patients with pneumonia compared with those in young patients. They also found that peripheral blood monocytes from healthy normal elderly subjects produced less amounts of these cytokines than those from healthy normal

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young subjects in response to lipopolysaccharide (LPS) stimulation [10]. In addition, IL-1 production by LPS-stimulated co-cultures of peritoneal macrophages and splenic T cells from old mice were markedly reduced when compared with cells of young mice [12] and TNF- α -induced MMP-9 expression was decreased in aortic smooth muscle cells derived from old mice [17]. Finally, mononuclear cells from elderly patients displayed a marked decrease in mitogen-stimulated production of interferon- γ (IFN- γ) and IL-2 [5]. These studies provide evidence that an age-dependent impairment of immune response results in diminished inflammatory responses to extracellular stimuli.

Radiation therapy has been commonly used for the treatment of brain tumors. About 200,000 individuals are treated with partial large field or whole brain irradiation every year in the US [15]. The prevailing evidence suggests that aging is an important prognostic factor in determining the response of brain tumors to radiation therapy [8]. Previous clinical studies showed that the use of high dose radiation therapy for brain tumors resulted in significantly lower survival rates for patients older than 70 years of age compared with those for patients aged 70 and younger [22,29]. In addition, Rosenblum et al. [23] reported that stem cells obtained from patients over the age of 50 with brain tumors were less sensitive to radiation than those from patients 50 years old or younger. Although the mechanisms for this effect have not been established, these studies clearly demonstrate that aging exerts a profound effect on the efficacy of radiation therapy for treatment of brain tumors.

It has been suggested that acute inflammatory responses in cancer patients undergoing radiation therapy may have beneficial effects. Indeed, a number of previous studies have demonstrated that an enhanced production of pro-inflammatory cytokines in response to radiation is a necessary component of normal tissue repair processes [24,27]. Although it is generally accepted that the immune responses and the effectiveness of radiation therapy decline with age, the association between aging, inflammation, and radiation therapy remains to be further investigated. Therefore, the present study was designed to examine the effect of age on radiation-induced expression of pro-inflammatory mediators, including several cytokines (e.g., TNF- α , IL-1 β , and IL-6), adhesion molecules (e.g., E-selectin, ICAM-1, and VCAM-1), the chemokine MCP-1, and MMP-9 in rat brain.

Male young (4 months of age), middle-aged (16 months of age), and old (24 months of age) F344 $\times$ BN rats were obtained from the NIA colony at Harlan Laboratories, Inc. (Indianapolis, IN). Animals were housed on a 12/12 light-dark cycle with food and water provided *ad libitum*. Animal experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23 revised 1996) and adequate measures were taken to minimize pain or discomfort. All studies were approved by the Institutional Animal Care and Use Committee.

Whole brain irradiation procedures were carried out as described previously with minor modifications [14]. Briefly, rats were anesthetized with a ketamine/xylazine mixture (80/12 mg/kg body weight) and received either whole brain irradiation with a single dose of 10Gy γ -rays or sham-irradiation. Whole brain irradiation was performed in a ^{137}Cs irradiator using lead and Cerrobend shielding devices to collimate the beam so that the whole rat brain, including the brain stem, was irradiated. Control rats were anesthetized but not irradiated. The animals were maintained for 4, 8, and 24 h post-irradiation. The brains were rapidly removed and the hippocampus was dissected, immediately frozen in liquid nitrogen, and stored at -80°C until analysis.

Quantitative real-time RT-PCR was employed for gene expression analyses [14]. Total RNA was isolated and reverse transcribed. Amplification of individual genes was performed on the Applied Biosystems 7300 System using TaqMan $^{\circledR}$ Universal PCR Master Mix and a standard

thermal cycler protocol. TaqMan® Gene Expression Assay Reagents for rat TNF- α , IL-1 β , IL-6, ICAM-1, VCAM-1, E-selectin, MCP-1, MMP-9, and GAPDH (housekeeping gene) were used for specific probes and primers of PCR amplifications. The threshold cycle (C_T) was determined and relative quantification was calculated by the comparative C_T method.

The statistical analysis of data was completed using SigmaStat 3.5 (SPSS Inc., Chicago, IL). One-way analysis of variance (ANOVA) was used to compare mean responses among the treatments. For each endpoint, the treatment means were compared using the Bonferroni least significant difference procedure. Statistical probability of $p < 0.05$ was considered significant.

The effect of aging on radiation-induced expression of the pro-inflammatory cytokines, TNF- α , IL-1 β , and IL-6 in rat brain is shown in Fig. 1. A single dose of whole brain irradiation dramatically increased mRNA expression levels of TNF- α (Fig. 1A), IL-1 β (Fig. 1B), and IL-6 (Fig. 1C) in hippocampus collected from rat brains for all age groups compared to their sham irradiated controls. However, in response to radiation overexpression of TNF- α and IL-6 was markedly attenuated at all time points in middle-aged and old rats compared with young animals. A significant age-dependent attenuation of TNF- α expression was detected in rat brains 8 h after irradiation (young rats, 9.1-fold induction; middle-aged rats, 3.3-fold induction; and old rats, 2.3-fold induction) and 24 h after irradiation (young rats, 1.8-fold induction; middle-aged rats, 1.1-fold induction; and old rats, 0.5-fold induction). A similar age-dependent decrease in IL-1 β expression in response to irradiation was observed 4 and 8 h after irradiation while the influence of age was not significant at the 24 h time point.

The effect of aging on radiation-induced expression of the adhesion molecules, ICAM-1, VCAM-1 and E-selectin, in hippocampus is shown in Fig. 2. A significant up-regulation of ICAM-1 (Fig. 2A), VCAM-1 (Fig. 2B), and E-selectin (Fig. 2C) mRNA expression was observed 4 and 8 h after irradiation in all age-groups compared with age-matched sham-irradiated controls. In contrast, expression levels of these adhesion molecules 4 and 8 h after irradiation were profoundly lower in middle-aged and old rats than those in young groups. A significant age-dependent attenuation of ICAM-1 and VCAM-1 expression was observed 4 h after irradiation (young rats, 21-fold induction; middle-aged rats, 14-fold induction; and old rats, 8.2-fold induction) and 8 h after irradiation (young rats, 2.6-fold induction; middle-aged rats, 2.2-fold induction; and old rats, 1.6-fold induction), respectively.

Radiation resulted in a significant and dramatic up-regulation of MCP-1 mRNA expression in hippocampus in all age-groups compared with their age-matched sham-irradiated controls (Fig. 3). Aging attenuated radiation-induced MCP-1 expression in brain at all age time points studied. A significant age-dependent impairment in MCP-1 expression was detected in rat brains 4 h after irradiation (young rats, 391-fold induction; middle-aged rats, 169-fold induction; and old rats, 98-fold induction).

We also addressed the effect of aging on radiation-induced expression of MMP-9 in rat brain (Fig. 4). Irradiation significantly up-regulated MMP-9 mRNA expression for all age groups 8 h after irradiation compared with their age-matched sham-irradiated controls. Previous *in vitro* and *in vivo* data demonstrated that irradiation increases mRNA expression and gelatinolytic activity of MMP-9 in brain [20,28]. Our recent *in situ* zymography result also showed strong gelatinolytic activity in rat brains after irradiation (unpublished data). These studies suggest that radiation-induced MMP-9 mRNA expression is consistent with the increase in MMP-9 activity in brain. Regardless of age, MMP-9 expression levels were not significantly different between sham and irradiated rat brains 4 and 24 h after irradiation. However, there was a significant age-dependent attenuation of radiation-induced MMP-9 expression in rat brains 8 h after irradiation (young rats, 2.4-fold induction; middle-aged rats, 1.6-fold induction; and old rats, 1.3-fold induction). Interestingly, the mRNA expression

pattern of MMP-9 is different from those of the other genes investigated in the present study. Since pro-inflammatory cytokines are known to up-regulate MMP-9 expression [19], it is possible that irradiation may indirectly result in overexpression of MMP-9 through induction of these cytokines. However, the exact mechanisms of the late response of irradiation-induced MMP-9 expression remain unclear and should be further investigated.

It is commonly accepted that chronic overexpression of pro-inflammatory mediators has detrimental effects on the brain [9]. However, more recent evidence demonstrated that acute overexpression of pro-inflammatory mediators may represent a coordinated response to promote regeneration and repair processes of damaged areas in irradiated brain [13]. In the present study, we examined the effect of aging on acute expression of pro-inflammatory mediators, including cytokines (e.g., TNF- α , IL-1 β , and IL-6), adhesion molecules (e.g., E-selectin, ICAM-1, and VCAM-1), the chemokine MCP-1, and MMP-9 in response to irradiation. A rat model of whole brain irradiation with a single dose of 10Gy was chosen because it is the lowest dose to have a clear radiation effect [30] and is below the threshold for vascular changes, demyelination, or radionecrosis [16]. Finally this dose is close to a clinically relevant dose in humans since the rat brain is more resistant to radiation injury than human brain [16]. We found that the expression of all pro-inflammatory mediators evaluated in the present study were significantly up-regulated in response to radiation compared with sham-irradiated control groups regardless of age. In contrast, a significant age-dependent attenuation of inflammatory responses to acute radiation exposure was observed. These data are consistent with the age-related impairments in immune and inflammatory responses to stimulation described in response to other acute stresses [4,25,31]. It is possible that reduced production of pro-inflammatory mediators in response to irradiation compromises the normal host defense mechanisms by decreasing the number of inflammatory cells in damaged brain tissue and subsequently leading to impaired repair/remodeling responses in old individuals. In addition, results from the present study may provide potential cellular and molecular mechanisms responsible for poor outcomes (e.g., survival and improvement in neurological function) in response to radiation therapy in elderly brain tumor patients.

It is widely accepted that basal expression levels of pro-inflammatory mediators including TNF- α , IL-1 β , and IL-6 are significantly elevated in the aged brain compared with younger subjects [25]. In contrast, advancing age results in a marked decrease in inflammatory responses induced by extracellular stimuli. A negative correlation between age and monocyte production of these cytokines in response to IFN- γ or LPS has been observed among different age groups of animals [31]. It was also found that LPS administration resulted in a significant attenuation of TNF- α and IL-6 mRNA expression in brains of old mice compared with those of young mice [25]. Finally, Bruunsgaard et al. [4] demonstrated an impaired production of pro-inflammatory cytokines including TNF- α and IL-1 β in response to LPS stimulation in elderly humans. Consistent with these previous reports, the present study also showed that aging is associated with an enhanced basal expression level of pro-inflammatory mediators and a diminished inflammatory response in brain to extracellular stimuli.

The pro-inflammatory pathways triggered by overexpression of inflammatory mediators have been implicated in the pathophysiological process of brain injury and subsequent progression of neurological disorders [6]. For example, amyloid beta (A β) peptides contribute to Alzheimer's disease (AD) pathology through an inflammatory cascade in the brain *via* production of cytokines (e.g., IL-1 β , TNF- α , and IL-6) and chemokines (e.g., MIP-1 α and MIP- β) [34]. It was also found that increased production of IL-1 β , TNF- α , and IL-6 was observed in the brains of patients diagnosed with AD [32]. The destructive processes including neurodegeneration, gliosis, and progressive neurological disease are mediated by overexpression of IFN- α , TNF- α , IL-1 β , or IL-6 [2]. Furthermore, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) markedly reduced the prevalence of AD in patients, raising

the possibility that an inflammatory environment in the brain has a significant role in the pathogenesis of central nervous system diseases [1].

On the contrary, more recent evidence suggests that acute overexpression of pro-inflammatory mediators are part of a complex pathway to resolve tissue injury [11,33]. For example, neuroprotective effects of pro-inflammatory cytokines, such as promotion of neuronal differentiation and survival, induction of neurotropic factors, and induction of anti-inflammatory mediators, were observed after acute traumatic brain injury (TBI) [18]. The beneficial role of cytokines in the pathophysiology of TBI is also supported by animal studies indicating that cytokine knockout mice and cytokine-receptor knockout mice exhibited higher mortality and enhanced tissue damage after experimental TBI [18,26]. In addition, the protective role of pro-inflammatory mediators in the early stages of wound healing has been extensively reported. For example, enhanced production of cytokines (e.g., IL-6, TNF- α , and IL-1 β) [13], adhesion molecules (e.g., ICAM-1 and VCAM-1) [3], chemokines (e.g., MCP-1) [7], and MMPs (e.g., MMP-9) [21] at the wound site promotes healing process of injured brain tissues. These studies provide compelling evidence that the acute induction of pro-inflammatory mediators in brain is an essential part of a pathway that induces a protective response to brain injury.

In conclusion, the present study demonstrated for the first time that whole brain irradiation-induced acute inflammatory responses, including overexpression of pro-inflammatory cytokines (e.g., TNF- α , IL-1 β , and IL-6), adhesion molecules (e.g., ICAM-1, VCAM-1, and E-selectin), the chemokine MCP-1, and MMP-9, in rat brain are significantly impaired in aged animals. The impaired response to irradiation with age appears to reveal a generalized attenuation of the cellular response to damage and a reduced capacity of aging tissues to induce essential repair systems necessary for cellular maintenance. Additionally, these data contribute to a better understanding of age-dependent changes in radiation-mediated immune and inflammatory responses in brain and may lead to the development of effective treatment strategies for brain tumor patients who are undergoing radiation therapy.

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Fig 1.

Effect of aging on mRNA expression of pro-inflammatory cytokines in rat brain in response to whole brain irradiation. F344 x BN rats (4, 16, and 24 months of age; n=4) received either whole brain irradiation with a single dose of 10Gy or sham-irradiation, and were maintained for 4, 8, or 24 h post-irradiation. The mRNA expression levels of TNF- α (A), IL-1 β (B), and IL-6 (C) in hippocampus were determined by quantitative real-time RT-PCR. Values represent mean $\pm$ SEM for each group. *p<0.05 vs. age-matched control; !p<0.05 vs. young rats; #p<0.05 vs. young and middle-aged rats.

Fig 2.

Effect of aging on mRNA expression of adhesion molecules in rat brain in response to whole brain irradiation. Experiments were carried out as described in Fig. 1. The mRNA levels of ICAM-1 (A), VCAM-1 (B), and E-selectin (C) in hippocampus were determined by quantitative real-time RT-PCR. Values represent mean $\pm$ SEM for each group. * p <0.05 vs. age-matched control; ! p <0.05 vs. young rats; # p <0.05 vs. young and middle-aged rats.

Fig 3.

Effect of aging on MCP-1 mRNA expression in rat brain in response to whole brain irradiation. Experiments were carried out as described in Fig. 1. The mRNA level of MCP-1 was determined by quantitative real-time RT-PCR. Values represent mean±SEM for each group. *p<0.05 vs. age-matched control; !p<0.05 vs. young rats; #p<0.05 vs. young and middle-aged rats.

Fig 4.

Effect of aging on MMP-9 mRNA expression in rat brain in response to whole brain irradiation. Experiments were carried out as described in Fig. 1. The mRNA level of MMP-9 was determined by quantitative real-time RT-PCR. Values represent mean $\pm$ SEM for each group. * p <0.05 vs. age-matched control; ! p <0.05 vs. young rats; # p <0.05 vs. young and middle-aged rats.