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Praca poglądowa/Review paper

Odpowiedź neuronalnych komórek macierzystych na napromienianie

Response of neural stem cells to ionizing radiation

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Streszczenie

W momencie narodzin, proces tworzenia nowych neuronów jest zatrzymany w większości obszarów mózgu. Jednak w zakręcie zębatym hipokampa i komorach bocznych, neurogeneza zachodzi przez całe życie dzięki obecności neuronalnych komórek macierzystych. Ta zdolność do tworzenia nowych komórek układu nerwowego przez cały okres życia pełni kluczową rolę w rozwoju poznawczym głównie w zdolności do uczenia się i pamięci. Neuronalne komórki macierzyste to multipotentne komórki, które cechuje zdolność do samoodnowy i różnicowania w wyspecjalizowane komórki układu nerwowego. Ze względu na wysoki potencjał proliferacyjny, są bardzo wrażliwe na promieniowanie jonizujące. Niniejsza praca poglądowa opisuje aktualną wiedzę na temat wpływu promieniowania jonizującego na biologię neuronalnych komórek macierzystych. Poszerzenie wiedzy na temat neurotoksyczności wywołanej promieniowaniem jonizującym na poziomie neuronalnych komórek macierzystych, może w przyszłości pomóc w przezwyciężeniu skutków ubocznych zachodzącej po terapii przeciwnowotworowej mózgu i pomóc w ochronie utrzymania neurogenezy.

Abstract

Adult neurons are believed to be in a state of growth arrest. The generation of neurons is complete at the time of birth in most of the brain regions. However neurogenesis is present throughout life in the dentate gyrus of hippocampus and the lateral ventricles due to the presence of neural stem cells (NSC). This postnatal neurogenesis in the hippocampus plays a critical role in a cognitive development mainly in learning and memory functions. NSC are self-renewing, multipotent cells that generate the neurons and glia of the nervous system. Due to their high proliferation, NSCs are highly sensitive to ionizing radiation. This review describes the current knowledge on the impact of ionizing radiation on neural stem cells biology. Widening the knowledge of the mechanisms involved in radiation-induced neurotoxicity at the level of NSC

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may help to overcome in the future the side effects occurring after anti-cancer therapies of the brain and help protect and maintain neurogenesis..

Słowa kluczowe: neuronalne komórki macierzyste, neurogeneza, radioterapia

Keywords: neural stem cells, neurogenesis, radiation therapy

Wstęp

- **Radiation therapy and NSC**

The primary goal of radiation therapy is to enhance the effectiveness of tumor killing together with sparing healthy tissue. While the relationship between radiation effects and dose is well defined at higher doses, the effects of doses below 0.5 Gy are still unclear. Even though the use of radiotherapy resulted in a significant increase in cancer survivors [1], it is important to investigate the potential negative long-term effects of radiation. Recent developments in the use of radiation in diagnostics and in radiation therapy, especially in developed countries, caused a significant increase in the average dose received annually from medical sources [2]. Considering that currently ionizing radiation is used more widely for diagnostics and for cancer therapy, and that patients treated with radiation survive longer, there is an increasing concern about the side effects of low-dose radiation exposure. In pediatric patients, the cranial irradiation is a useful tool for a therapy of primary brain tumors [3]. However, during the radiotherapy, the surrounding normal tissues receive part of the treatment dose, typically due to scattered irradiation [4]. Due to prolonged survival, children with brain tumors manifest late effect of radiotherapy. Higher doses of radiation (≤45 Gy) cause a morphological changes, while lower doses (≤ 10Gy) represent more subtle changes like cognitive deficit. Those radiation-induced neurocognitive deficits are mostly problematic to pediatric patients where they cause memory and learning dysfunctions [5, 6]. The neurocognitive deficits after irradiation are incompletely understood. Neuroimaging studies in children who received cranial radiotherapy exhibit changes in brain structure. It has been shown, that radiation induces a loss in the proliferative capacity of neuronal precursor cells in the hippocampus [7]. Moreover, radiation is known to inhibit neurogenesis in hippocampus. This suggests that the potential cause of neurocognitive dysfunction may be due to depletion of the neural stem cells (NSC) required to form new neurons [8]. Normal adult neurons and glial cells which are terminally differentiated, exhibit a substantial radioresistance. On the contrary, NSC are very sensitive to ionizing radiation [7, 9]. Clinical observation and experiments on animal models revealed, that cranial irradiation of brain tumors results in cognitive dysfunction mainly due to inhibition of the proliferation and death of neural stem cells [5, 7, 9, 10]. Neural stem cells are primary cells characterized by their ability to self-renew and differentiate into neurons, astrocytes and oligodendrocytes. In the brain, NSC are present in the subventricular zones lining the lateral ventricles and in the subgranular zone of the hippocampal dentate gyrus. Mature neurons are considered to be in a state of growth arrest. The generation of neurons is complete at the time of birth in most of the brain regions. However in specific regions of hippocampus where neuronal stem cells are present, neurogenesis is observed through life [11]. This postnatal neurogenesis in hippocampus plays a critical role in cognitive development mainly in learning and memory functions.

- **Low-dose effect on NSC**

Induction of new techniques to radiotherapy is driven by a need of elevating radiation dose to tumor and deliver this dose more accurately [12]. Due to nature of radiation, elevating the dose in the target can cause that higher doses are distributed to surrounding organs/tissues. The absorption of dose in the places outside the beam is caused by scattered radiation consisting photons, electrons and neutrons [13]. Those low doses may cause unwanted effects, including clinical side effects. International Commission of Radiological Protection (ICRP) announced that no less than 300 mGy of radiation appears to cause disorders in the fetal brain [14]. Nevertheless few reports showed the effect of less than 300 mGy of radiation on brain

development. In mouse model, low-dose radiation of 100 mGy caused neuronal apoptosis in mouse cerebral cortexes on embryonic day 13.5 [15]. Moreover the DNA double strand breaks and apoptosis were induced in the ventricular and subventricular zones of mouse embryo [16]. It was also shown that 496 mGy of irradiation caused a significant decrease in the MAP-2 positive cells and neurite length [17]. Thus understanding of the differences between effects induced by different doses and dose-rates of radiation and the impact they may have on neuronal cancer stem cells is crucial for properly predicting the risks of low-dose radiation on the NSC potential to differentiate.

- **Bystander effect on NSC**

Besides the direct effects of radiation on cancer cells, radiotherapy can also modify the tumor microenvironment, which could thereby affect tumor development. The non-targeted effects of radiation are mediated by immune-signaling mediated mechanisms, which affect surrounding non-irradiated cells. This non-targeted effect in unirradiated cells is known as the radiation-induced bystander effect (RIBE), which is mediated by gaps in the junctions between the cells and through mediators released from irradiated cells, mainly cytokines and chemokines [18]. It has been reported that for cranial irradiation of brain tumors, NSC could be a bystander target [7, 10]. Neurogenesis depends on a microenvironment and signaling between multiple cell types, and irradiation could affect these interactions [7]. The precise effect of this process has not yet been identified. However it has been suggested that chronic inflammatory changes between precursor cells and the microvasculature play a role in this process [7]. Ivanov et el pointed out that understanding the intrinsic cellular communication between cancer and non-cancer cells, especially after radiation exposure, is highly desirable for development of strategies to either minimize or prevent the harmful radiation effect on normal stem cells. Ivanov et al showed that the intracellular communication between glioblastoma cells and bystander NSC could be involved in the amplification of cancer pathology in the brain. They proved that the cellular signaling triggered by radiation exposure in cancer cells can produce adverse effects on the integrity and function of NSC [19]. Treatment of NSC for 8 hours with medium from irradiated glioblastoma cells (5 and 10 Gy in a single dose) selectively suppressed the differentiation of NSC into neurons but not into astrocytes. Moreover it has been demonstrated that radiation-induced apoptosis of NSC in cell culture is mediated by TRAIL/TRAIL-R2 interactions through autocrine and paracrine stimulation. It created killing of both directly irradiated and bystander NSC. Furthermore, bystander suppression of NSC differentiation was most pronounced in case of radiation-induced intracellular communication between irradiated cancer cells and NSC [20].

Conclusions

Understanding the molecular mechanisms of response to low dose radiation is crucial for the proper evaluation of risks and benefits that stem from these exposures and should be considered in the radiotherapy treatment planning and in determining the allowed occupational exposures. We believe that widening the knowledge of mechanisms involved in radiation-induced neurotoxicity at the level of neural stem cells may help to overcome in the future the side effects occurring after anti-cancer therapies of the brain and help to protect and maintain neurogenesis.

Konflikt interesu/ Conflict of interest

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Piśmiennictwo / References

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