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Colony stimulating factor-1 receptor as a treatment for cognitive deficits postfractionated whole-brain irradiation

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Abstract:

Whole-brain irradiation (WBI) is commonly used to treat primary tumors of the central nervous systems tumors as well as brain metastases. While this technique has increased survival among brain tumor patients, the side effects of including a decline in cognitive abilities that are generally progressive. In an effort to combat WBI side effects, researchers explored the treatment of colony stimulating factor-1 receptor (CSF-1R) inhibitor. Data show that when a CSF-1R inhibitor is administered with fractionated WBI treatment, there is a decline in the number of resident and peripheral mononuclear phagocytes, a decrease in dendritic spine loss and a reduction in functional and memory deficits. CSFR-1R inhibitors have displayed promising results as an effective counter-treatment for WBI-induced deficits. Further research is required to optimize treatment strategies, establish a treatment timeline and gain a better understanding of the long-term side effects of targeting CSF-1R as a treatment strategy for WBI symptoms. This paper is a review article. Referred literature in this paper has been listed in the references section. The datasets supporting the conclusions of this article are available online by searching various databases, including PubMed. Some original points in this article come from the laboratory practice in our research center and the authors' experiences.

Keywords:

Brain metastases, colony stimulating factor-1 receptor inhibitor, microglia, primary central nervous system tumor, whole brain irradiation

Introduction

Primary tumors of the central nervous system (CNS) and brain metastases may be treated with whole-brain irradiation (WBI) (often delivered in 25–30 fractions for a total dosage of 55–60 Gy). The novel, enhanced treatments have resulted in lowered mortality rates but increased risks of detrimental side effects. In particular, progressive symptoms related to cognitive function present in approximately 50%–90% of long-term survivors (>6 months) after WBI treatment.^[1] There is little treatment available for patients suffering from these

cognitive abnormalities, as the cause of them is currently unknown. One dose of 10 Gy WBI causes periphery monocytes to gather in the CNS after 7 days of the single dosage.^[2] Similarly, research shows that WBI initiates the actions of immune cells expressing MHCII, CD11c, and CD3.^[3] Even though one study^[4] did not see monocyte-derived macrophages in the WBI treated adult brain, this may be because of varying sources of radiation or discrepancies in monocyte quantification. This study shows that in combination with a certain colony stimulating factor-1 receptor (CSF-1R), fractionated WBI treatment (fWBI) improves functional outcomes by decreasing the amount of resident and peripherally-derived

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mononuclear phagocytes and inhibiting the development of memory problems and dendritic spine loss (in mice).^[5]

Modulating Whole-brain Irradiation-induced Cognitive Deficits: microglia or Monocytes?

CSF-1 signaling plays a major role in the development and function of mononuclear phagocytes.^[6] Because of its receptor, CSF-1R, is expressed on the surface of CNS microglia and periphery monocytes, CSF-1R inhibition affects both cell types. Certain dosages of CSF-1R inhibitors can decrease the amount of microglia in mice. There is a 30%–50% reduction in microglia with a 300 ppm dose of PLX5622, a CSF-1R inhibitor,^[5,7] and a nearly complete elimination (>95%) of microglia with either a 1,200 dose of PLX5622 or a 290 ppm dose of PLX3397 (an inhibitor similar to PLX5622).^[8] Both levels of microglial depletion block WBI-induced dendritic spine loss and prevent the development of cognitive disabilities.^[5,9] Dendritic spine loss becomes apparent between 2 weeks and a month (the point where cognition is measured) following fWBI and continues until several months posttreatment.^[5,10] Despite knowing that radiation stimulates microglia and peripherally derived monocytes,^[2,11] it is unclear why WBI and fWBI cause dendritic spine loss. WBI increases the brain's concentration of chemoattractant cytokine CCL2, a molecule that stimulates CNS uptake of peripherally derived CCR2+ monocytes.^[12] CCR2 is a chemokine receptor absent from brain microglia^[2] and the stimulation of CCR2-CCL2 signaling causes the accumulation of CCR2-expressing monocytes (also known as "inflammatory monocytes") in the injured tissue. These CCR2-expressing monocytes then transform into macrophages with proinflammatory properties.^[13] Conversely, a lack of CCR2 molecules impedes the movement of CCR2+ Ly6Chigh from the bone marrow to the blood stream^[14] and reduces the WBI-induced neural and cognitive deficits.^[11] Ly6Chigh monocyte concentrations are reduced in the blood by PLX5622 treatment and in the CNS by CSF-1R antagonism, whereas Ly6Clow concentration is not affected.^[5] In the peripheral nervous system (PNS), Ly6Chigh differentiate into macrophages or dendritic cells within damaged tissues. It is postulated that in neuroinflammatory models (such as those for traumatic brain injury and multiple sclerosis), Ly6Chigh monocytes regulate inflammatory responses of the CNS and that microglia aid in tissue restoration.^[14] Stimulation of these monocytes and microglia possibly enhances neuronal damage post-WBI, but the degree of influence these cells have on neuroinflammation following WBI and fWBI is currently unclear. Additional studies are warranted to examine the specific cell phenotypes mediating the learning and memory performance.

Colony Stimulating Factor-1 Receptor Inhibition as Potential Therapy to Prevent Whole-brain Irradiation-induced Cognitive Deficits

While CSF-1R inhibition remains one of the principal ways to treat and prevent cognitive deficits post-WBI treatment, more studies are needed to elucidate the treatment's safety, effectiveness, and mechanism of action. First, the function of CSF-1R signaling differs depending on age. Because CSF-1R is naturally expressed in cortical neurons, immature neurons, neural progenitor cells, and following chemical injury, CSF-1R treatment under these conditions may have a direct effect on neural function.^[6] Second, CSF-1R treatment may produce different effects regarding inflammation in the CNS, as well as in the PNS due to monocytes expressing both CSF-1R and CCR2 and microglia expressing only CSF-1R. CSFR-1 inhibition most likely decreases microglia concentration, but its effects on monocytes and peripheral immune responses is widely unknown. PLX5622 treatment caused a nearly 30% reduction in Ly6Chigh monocytes but scarcely affected Ly6Clow monocytes in humans. Other results display a decrease in nonclassical CD14⁺ CD16⁺ monocytes but not the classical CD14⁺ CD16⁻ monocytes following treatment with the CSF-1R antibody.^[15] Small inhibitors opposing the antibody, specificity of the inhibitor and antibody, or varied reactions to CSF-1R inhibition in rodents and humans may cause the discrepancies between the classical and nonclassical monocytes. In addition, little is known about the relationships between CSF-1/CSF-1R and CCL2/CCR2 signaling pathways. Third, cognitive deficits generally appear months to years following WBI treatment. While it is unknown if CSF-1R inhibition during irradiation can prevent chronic cognitive abnormalities, several animal studies displayed CSF-1R inhibition to last between 7 days and 12 weeks. Since macrophages' roles differ depending on their microenvironments, infiltrating monocytes and macrophages may change their function from small scale repair to long-term restoration. More studies need to examine the therapeutic window and long-term effects of CSF-1R treatment. Finally, even though WBI treatment is primarily used on brain tumor patients, the majority of studies focus on normal brains due to the additional treatments brain tumor patients often require. CSF-1R inhibitors may interfere with other treatments and the tumor microenvironment of brain-tumor patients, as CSF-1R inhibition primarily affects tumor related macrophages. Even though over 50% of tumors recur after CSF-1R treatment,^[16] the inhibitor also appears to prevent glioma development and interact with the tumor's macrophages.^[17] More preclinical studies need to be conducted in brain tumor models to examine cognition following CSF-1R inhibitor treatment.

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Conflicts of interest

There are no conflicts of interest.

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