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Recent progress in the elucidation of the mechanisms of chemotherapy-induced cognitive impairment

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Abstract. – The term "chemobrain" refers to the cognitive dysfunction that occurs after chemotherapy, and it is also known as chemotherapy-induced cognitive impairment or "chemofog". The aim of this review is to bring together the findings of existing literature on the topic and summarize the current knowledge on the potential mechanisms of chemobrain. According to the reviewed studies, the mechanisms by which chemotherapy could cause chemobrain include disruption of hippocampal cell proliferation and neurogenesis, hormonal changes, increased oxidative stress and reactive oxygen species production, chronic increase in inflammation, and alterations in synaptic plasticity and long-term potentiation. While the effects of inflammation and oxidative stress on neurogenesis and their role in chemotherapy-induced cognitive impairment have been widely studied, the chemotherapy-induced cognitive impairment mechanisms that involve mitochondrial dysfunction, estrogen dysregulation, and increased transglutaminase 2 are still unclear. Further studies on these mechanisms are necessary to understand the effects of chemotherapy at the cellular and molecular level and facilitate the development of preventive and therapeutic strategies against chemotherapy-associated cognitive impairment or chemobrain.

Key Words:
Chemotherapy-induced cognitive impairment, Chemobrain, Chemotherapy, Neurophysiology.

Introduction

Chemotherapy is a standard treatment for cancer that has been in use since the early 20th century[1]. The aim of chemotherapy is to reduce the cellular proliferation of tumor cells[2]. According to their target in tumor cells, chemotherapeutic agents are classified as those that disrupt DNA, RNA, or protein biosynthesis[3]. Additionally, based on their mechanism of action and chemical structure[4,5], they are classified as alkylating agents, such as cyclophosphamide; methotrexate antimetabolites, such as 5-fluorouracil; and anthracyclines, such as doxorubicin. In addition, hormonal therapy drugs, such as tamoxifen and anastrozole, are a class of drugs that regulate and prevent cancer cell proliferation by inhibiting hormone receptors[6]. Chemotherapy is known to be effective in cancer treatment, but it is often accompanied by adverse effects such as fatigue[7], loss of appetite, stress, and inflammation[8], which eventually affect patients' quality of life[9], and can even cause cognitive dysfunction[10,11].

The cognitive impairment that occurs as a result of chemotherapy for cancer is also known as chemobrain or chemofog[12] and is recognized as a complication of chemotherapy for cancer[13-15]. Cognitive impairment is observed in up to 75% of patients who have undergone chemotherapy for cancer, and it persists after treatment in 17-34% of survivors. For example, one study[16] showed that breast cancer survivors who had received chemotherapy performed more poorly on a set of neuropsychological tests than matched healthy controls even 20 years after treatment. Chemobrain has been diagnosed since the 1970s; however, this condition was not clearly described or characterized until the 1990s. Chemobrain affects different aspects of memory function, and its symptoms include memory loss, inability to concentrate, difficulty in processing information, and other subtle cognitive changes[12,17,18]. Various studies[19-21] have shown that chemotherapeutic drugs affect the function and structure of the brain, as well as alter signaling pathways in neuronal cells. The most common areas of the brain that are affected by chemotherapy are the frontal lobes and parts of the limbic area, particularly the hippocampus. With regard to the mechanisms of chemobrain,

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some chemotherapeutic agents, such as cyclophosphamide, can permeate the blood-brain barrier (BBB) and have a direct neurotoxic effect on the brain[15,22,23]. Others, such as doxorubicin, cannot permeate the BBB, but might induce chemobrain indirectly[20,24,25]. Although there have been several clinical and experimental studies on the chemobrain phenomenon, the underlying mechanisms and the resulting cognitive problems are poorly understood.

In this review, we discuss some recent studies[26-31] that provide insights into the possible mechanisms by which chemotherapy could cause chemobrain, including the disruption of hippocampal cell proliferation and neurogenesis[26,27], hormonal changes[28], increased oxidative stress and reactive oxygen species (ROS) production[29], chronic increase in inflammation[30], and alterations in synaptic plasticity and long-term potentiation (LTP)[19,31] during and after chemotherapy (Figure 1). Through this review, we aim to improve our understanding of the mechanisms underlying chemobrain, as this could help in the development of preventive strategies to ameliorate the adverse effects of chemotherapy.

Anatomical Basis of Chemobrain

There is evidence to show that chemotherapy affects cognitive function *via* its effect on certain areas of the brain. An animal study[32] on a mouse model found that chemotherapy (along with tumor growth) resulted in considerable reduction in the volume of the hippocampus and frontal lobes. Accordingly, Inagaki et al[29] (2007) showed that in breast cancer survivors, one year after chemotherapy, smaller grey matter volumes were observed in the right prefrontal cortex and para-hippocampal gyrus, and smaller white matter volumes were observed in the bilateral middle frontal gyri, left para-hippocampal gyrus, left precuneus, and right cingulate gyrus. Similarly, a study[33] on children with lymphoblastic leukemia who underwent intrathecal and systemic chemotherapy showed that the volumes of the bilateral hippocampi, the left nucleus accumbens, amygdala, and thalamus were significantly smaller after treatment. These changes in brain structure have a corresponding effect on the function of the affected areas. For instance, prospective longitudinal studies[34,35] showed that chemotherapy resulted in a decrease in working memory-related brain activity in the frontal lobes one month after treatment, although the patients partially recovered a year later. Further, in patients with breast cancer, chemotherapy was found to decrease brain activation in regions of the parietal lobe that were involved in planning and episodic memory 10 years after treatment[36]. With regard to the effects of chemotherapy at the cellular level, the chemotherapeutic drugs carmustine, cisplatin, and cytosine arabinoside were associated with in-

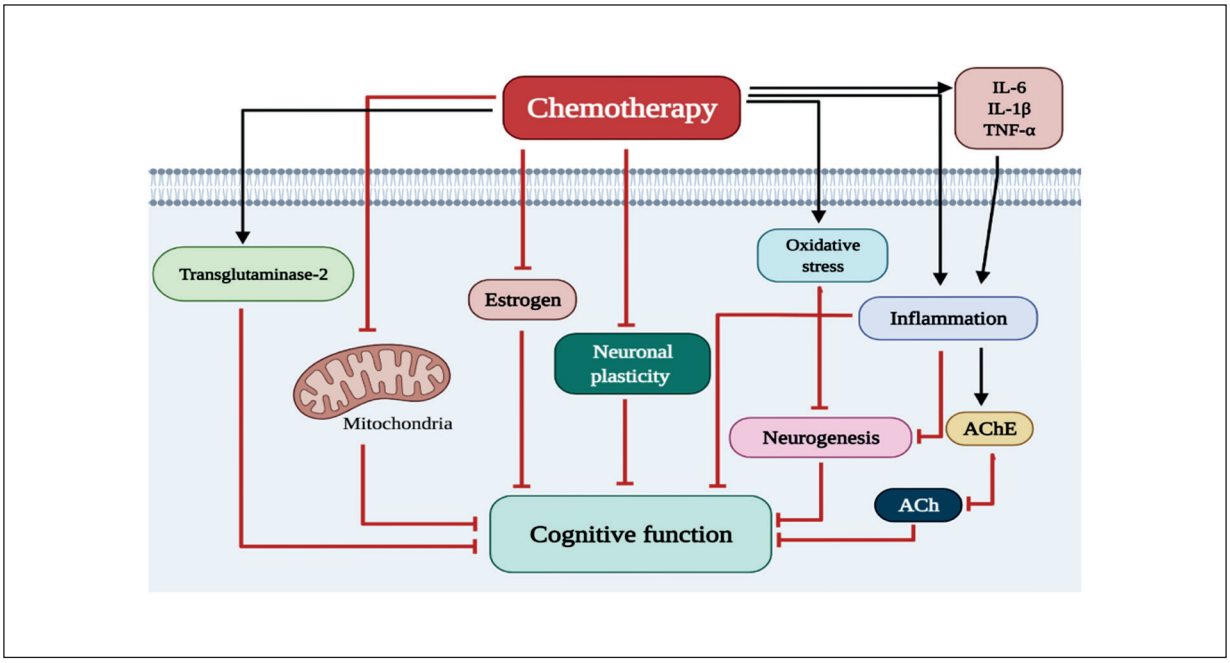

Figure 1. Mechanisms of chemotherapy-induced cognitive impairment.

creased cell death and decreased cell division in the subventricular zone, in the dentate gyrus of the hippocampus, and in the corpus callosum of the central nervous system (CNS)[37]. These effects on neurogenesis can cause changes in the neuronal architecture to eventually affect CNS function. This notion is supported by a study on mice which showed that chronic treatment with adriamycin and cyclophosphamide altered the neuronal architecture in the hippocampus via a significant reduction in total dendritic length, ramification, and complexity, as well as spine density and maturation in hippocampal neurons[38]. This finding is supported by another study which demonstrated loss of dendritic spines and synapses in hippocampal neurons even in response to low doses of cisplatin in rats[39]. Another important anatomical change induced by chemotherapy is alteration in functional connectivity between different areas of the brain. For example, breast cancer survivors appeared to have disrupted functional connectivity in the frontal, temporal, and striatal brain regions five years after chemotherapy[40]. Additionally, Chen et al[41] (2017) found decreased functional connectivity between the dorsolateral prefrontal cortex and the right hippocampus in breast cancer patients treated with tamoxifen, and Cheng et al[42] (2017) found a chemotherapy-induced decrease in hippocampal functional connectivity between the left hippocampal network and the right parahippocampus, and between the right hippocampal network and the left temporal pole in breast cancer survivors. All these findings indicate that the cognitive effects of chemotherapy have a strong anatomical basis that could be a starting point for understanding the underlying molecular mechanisms.

Chemobrain and Neurogenesis

Adult neurogenesis is an evolutionarily conserved process in several species, including rodents and humans[43]. Under normal conditions, active adult neurogenesis is primarily limited to two brain regions: the subgranular zone of the hippocampus and the dentate gyrus, and the subventricular zone of the lateral ventricles[44]. Learning and memory processes enhance neurogenesis in these regions, and spatial memory tasks specifically enhance hippocampal neurogenesis[45]. Oxidative stress causes memory impairment and reduces hippocampal neurogenesis[46]. Importantly, chemotherapeutic drugs can also reduce hippocampal neurogenesis and cause cognitive impairment[18,47,48], but the underlying mechanisms have not been fully elucidated.

It has been hypothesized that chemotherapeutic drugs that cross the BBB cause a reduction in neurogenesis and lead to cognitive impairment[27]. The chemotherapeutic drugs cyclophosphamide, methotrexate, and fluorouracil, which can permeate the BBB, resulted in a 20% decrease in hippocampal cell neurogenesis that was probably caused by changes in histone modification in the hippocampus, that is, an increase in histone acetylation and a decrease in histone deacetylase activity[26]. Chemotherapeutic agents that cannot cross the BBB, such as paclitaxel and doxorubicin, also produce a similar reduction in neural cell proliferation and neurogenesis[26,27,49]. However, the mechanism by which chemotherapeutic drugs that are unable to cross the BBB affect cognitive function remains unknown. Some studies[50,51] have explored the mechanisms that are likely to be involved in their effects. For example, one study showed that a combination of doxorubicin and cyclophosphamide reduced the mRNA expression of nicotinic acetylcholine receptor[50]. In addition, a reduction in glutamate uptake in the mouse frontal cortex and hippocampus and a consequent increase in glutamate levels were observed in another study[51]. Although glutamate plays a major role in regulating cognitive function, chronic excessive levels could lead to neurotoxicity and neurodegenerative disease[52,53]. Glutamate levels could increase as a result of other mechanisms, such as an increase in tumor necrosis factor-α (TNF-α) levels[54]. Increased TNF-α levels have been reported during doxorubicin treatment and could inhibit excitatory amino acid transporter 2 (EAAT2) to ultimately cause an increase in glutamate levels. Thus, this TNF-α/EAAT2/glutamate pathway might be involved in the reduction in hippocampal neurogenesis and the resulting chemobrain associated with chemotherapeutic agents that cannot permeate the BBB.

Another factor that could potentially play a role in the mechanism of chemobrain is insulin-like growth factor 1 (IGF-1). IGF-1 is a polypeptide hormone with a similar structure to insulin. IGF-1 is primarily synthesized in the liver, and acts as a downstream target of growth hormone[55]. IGF-1 activates different signaling pathways, such as the mitogen-activated protein kinase and phosphatidylinositol 3-kinase signaling pathways[56,57], which are involved in many cellular and physiological processes including differentiation, proliferation, development, survival, apoptosis, and cognition[58-60]. IGF-1 activity is reduced during

aging[61,62]. Serum IGF-1 levels were also found to decrease by 10% after chemotherapy for breast cancer, but the IGF-1 levels rapidly returned to normal[63]. Additionally, when IGF-1 was administered in mouse models of chemobrain that were treated with cyclophosphamide, fluorouracil, doxorubicin, and paclitaxel, hippocampal neurogenesis was partially revived. This indicates that IGF-1 might have potential for therapeutic application in the prevention of chemobrain after chemotherapy for cancer[64].

Chemobrain and Oxidative Stress

Excessive oxidative stress in the brain is one of the causes of cognitive impairment[65]. The formation of ROS and other free radicals during metabolism is an essential and regular process that is typically balanced by an endogenous antioxidant system[66]. However, excessive production of free radicals results in oxidative stress, which is responsible for oxidative injury of neurons and membranes due to lipid peroxidation and eventually results in cellular damage[67].

The US-FDA has approved 132 chemotherapeutic drugs, of which 56 have the potential to induce oxidative stress[68]. For example, doxorubicin led to excess production of ROS[69], which are known to be neurotoxic at high concentrations[20]. Accordingly, doxorubicin was also associated with cognitive dysfunction[24], even though it is unable to cross the BBB. Thus, the cognitive impairment associated with doxorubicin is probably caused by excessive ROS generation. Further, doxorubicin has also been found to reduce neurogenesis, and this effect could be associated with excessive ROS generation and increased lipid peroxidation that led to neuronal apoptosis and, eventually, cognitive dysfunction[70].

The N-methyl-D-aspartate (NMDA) receptor is a glutamate receptor that is required for synaptic plasticity, learning, and memory. It modulates calcium ion entry into the neuron and the subsequent cascade that culminates in increased transcription[71]. Oxidative stress upregulates NMDA receptor function and expression on the cerebrovascular endothelium, and this causes disruption of the BBB[72] and, consequently, the passage of neurotoxic compounds into the brain[73]. A pharmacokinetic study[74] showed that low concentrations of doxorubicin can cross the BBB during chemotherapy. However, it is unlikely to induce apoptosis in the brain at such low concentrations. Therefore, the mechanisms by which chemotherapy affects the BBB are unclear and need to be studied, particularly in terms of its direct and indirect effects on the decrease in neurogenesis.

Chemobrain and Neuroinflammation

Inflammation is one of the mechanisms underlying cognitive impairment[75]. Inflammation has been associated with neuropathological processes related to the development of Alzheimer disease and dementia[76]. Further, inflammation, cytokine levels, and cognitive dysfunction are closely associated[77]. Several chemotherapeutic drugs can promote inflammation[30]. For instance, cyclophosphamide, which is commonly used to treat brain tumors, can cross the BBB and induce hippocampal inflammation[78], thereby disrupting hippocampus-dependent memory tasks[79]. Inflammatory cytokines, such as TNF-α, interleukin (IL) 6, and IL-1β, play an important role in regulating brain function[80], and high levels of these cytokines lead to changes in cognitive function[81-83]. In fact, an increase in the levels of cytokines has been speculated to be one of the causes of chemobrain. Additionally, peripheral cytokines can also cross the BBB and induce the release of central cytokines that lead to cognitive impairment[84,85]. For example, doxorubicin peripherally induces the production of TNF-α, which crosses the BBB, enters the brain, and enhances TNF-α release centrally, eventually causing cognitive impairment[20]. Further, altered glucose metabolism is observed in the hippocampus and brain cortex in diabetes and Alzheimer's disease[86,87]. Based on this finding, it is speculated that one of the mechanisms of chemobrain could be inflammation-induced reduction in glucose metabolism in the hippocampus that leads to spatial memory impairment[88].

Acetylcholine (ACh) is a neurotransmitter that plays a significant role in the regulation of several physiological functions, including synaptic plasticity and cognitive function[89]. Behavioral and electrophysiological studies have shown that nicotinic acetylcholine receptor stimulation improves memory function in several conditions such as Alzheimer disease, stress, and sleep deprivation[90-92]. Nicotine also enhances glutamatergic transmission by activating alpha-7 nicotinic receptors in the hippocampus, thereby activating hippocampal function[93,94]. Acetylcholine is metabolized primarily by enzymatic hydrolysis through acetylcholinesterase (AChE)[95]. The first line of treatment for Alzheimer disease includes AChE inhibitors, such as donepezil, galantamine,

and rivastigmine, which increase ACh levels in the brain and thereby slow disease progression[96]. Interestingly, pro-inflammatory cytokines such as IL-1β impair cognitive function by increasing AChE levels[97,98]. Based on these findings, one of the mechanisms underlying chemobrain could involve inflammation-induced increase in cytokine levels that subsequent causes an increase in AChE activity.

Chemobrain and Neuronal Plasticity

Long-term potentiation (LTP) is a considered as a measure of the strength of synapse activity, which is an indicator of learning and memory formation, and it is defined as a persistent increase in the excitatory postsynaptic current following stimulation[99]. The hippocampus is responsible for learning and memory consolidation, and these processes occur because of changes in the synaptic structure, which are also referred to as synaptic plasticity[100]. Several studies have examined the effects of chemotherapy on LTP[19,31]. In certain types of cancer, however, it is challenging to distinguish whether memory impairment is caused by chemotherapy or is an adverse effect of the cancer.

Several studies have evaluated learning and memory at different time points after cyclophosphamide treatment[31]. The Morris water maze, T-maze techniques, and novel location recognition are some of the tests that were used to evaluate spatial memory in rodents[22,31]. In one such study, LTP was used to measure synaptic plasticity and strength[31] with the Schaffer collateral pathway during cyclophosphamide treatment, and after 8 and 53 weeks of recovery in rats. The findings showed that LTP was not induced during cyclophosphamide treatment, and the LTP response was higher than that in the controls after 8 and 53 weeks of recovery[31]. Alhowail et al[19] (2019) evaluated the effect of doxorubicin treatment on brain slices by using a low concentration of doxorubicin that is similar to the concentration which reaches the brain under in vivo conditions, and they showed that doxorubicin reduces LTP in a dose-dependent manner. Thus, one of the mechanisms underlying chemobrain is probably a reduction in synaptic plasticity.

Chemobrain and Mitochondrial Function

Mitochondria are present in the cytoplasm of most eukaryotic cells, including neurons[101], and play a vital role in energy production, calcium regulation, cell metabolism, and synaptic transmission[101-103]. Mitochondria contain their own genome in the form of mitochondrial DNA, which encodes important subunits of the respiratory chain, where electrons are combined with oxygen to enable the flow of energy through the mitochondria[104]. The energy produced by mitochondria is stored in the form of the small molecule adenosine triphosphate or ATP, which is used in endocytosis, ion transport, and biosynthesis of ROS and neurotransmitters[105,106]. Mitochondria also respond directly to extracellular signaling: for example, estrogen and its receptors modulate ROS and calcium levels *via* mitochondria[107]. Mitochondrial dysfunction is associated with several diseases and aging[108], and can cause cognitive impairment, particularly in hippocampus-dependent tasks such as learning and memory formation[109]. Interestingly, several chemotherapeutic agents, such as doxorubicin, cisplatin, and cyclophosphamide, can induce cognitive impairment via mitochondrial dysfunction[110-112]. Other chemotherapeutic agents, such as trastuzumab, sunitinib, and methotrexate, have been found to induce mitochondrial dysfunction in the kidney[113], there have been very few studies on the association between these drugs and the onset of chemobrain.

Chemobrain and Transglutaminase 2

Transglutaminase 2 (TG2) is the most widely distributed and abundantly expressed member of the transglutaminase family of enzymes[114], which comprises a group of intracellular and extracellular proteins that catalyze Ca^{2+}-dependent posttranslational modification of proteins[115]. TG2 regulates several functions such as cell adhesion; protein disulfide isomerase, kinase, and scaffold activities; and cell growth, differentiation, and apoptosis[116]. TG2 also plays an important role in the regulation of cognitive function and neurodegenerative disease progression[116,117]. Increase in TG2 activity in the brain could cause memory impairment[118]. The association between chemotherapy, cognitive function, and TG2 activity is unclear. However, some chemotherapeutic agents, such as doxorubicin, can cause an increase in TG2 activity[119] and could potentially cause memory impairment. Further studies are required to clarify the association between chemotherapy, TG2 activity, and cognitive function.

Chemobrain and Estrogen

Estrogen is an important steroidal sex hormone involved in many signaling pathways in the hu-

man body[120]. The biosynthesis of estrogen is mediated by aromatase, which converts androgen to estrogen[121]. Estrogen is released by the adrenal cortex, which is stimulated by the hypothalamus. The hypothalamus releases adrenocorticotropic hormone, which stimulates the adrenal cortex, causing the biosynthesis and release of estrogen[122]. Estrogen binds to estrogen receptors, which belong to the steroid hormone superfamily of nuclear receptors, and have α and β isoforms[123]. Estrogen has shown neuroprotective effects in the central nervous system against injuries, such as traumatic brain injury and ischemic brain injury, in rodent models[124,125]. Additionally, estrogen plays an important role in cognitive function[126]. Estrogen receptors are found in many areas of the brain that are associated with cognition, including the hippocampus, prefrontal cortex, and amygdala[127], and therefore, probably play an essential role in regulating learning, memory, and synaptic plasticity[128]. However, the exact molecular mechanisms underlying the neuroprotective effects of estrogen are not fully understood.

Endocrine therapies are one of the most common adjuvant therapies used in the treatment of breast cancer. The drugs used in this therapy include aromatase inhibitors, such as anastrozole, and estrogen receptor blockers such as tamoxifen[6]. A reduction in estrogen levels and blockage of estrogen receptors are associated with cognitive impairment[129-131]. Therefore, based on what is currently known about the mechanisms by which estrogen and estrogen receptors affect cognitive function, it is possible that aromatase inhibitors and estrogen receptor blockers cause or exacerbate chemobrain.

Conclusions

Chemobrain is one of the most common complications of chemotherapy, and it has a considerable effect on a patient's cognitive abilities and, consequently, their quality of life. To reduce the incidence of chemobrain and prevent its occurrence in patients undergoing chemotherapy, the mechanisms by which chemobrain occurs must be elucidated. Research on the link between adverse effects of chemotherapy and cognitive dysfunction is ongoing, but the causes and mechanisms of chemobrain are poorly understood. This study has reviewed the relevant papers published on this topic to bring together what is known about the mechanisms of chemobrain:

- Chemobrain has a strong anatomical basis: it affects the frontal lobes, limbic system, central functional connectivity, and hippocampal neuronal architecture.
- Chemotherapeutic drugs that can cross the BBB, such as cyclophosphamide, affect neurogenesis via histone modifications. On the other hand, chemotherapeutic drugs that cannot cross the BBB, such as doxorubicin, indirectly affect neurogenesis via pathways that involve TNF-α, EAAT2, and glutamate.
- Several chemotherapy drugs are associated with an increase in oxidative stress, which causes neuronal injury and, therefore, impacts neurogenesis and cognitive function. In turn, there is some preliminary evidence to show that oxidative stress disrupts the BBB, and this causes neurotoxic substances to permeate the BBB.
- In terms of inflammatory mechanisms, chemobrain could be caused by an inflammation-induced reduction in glucose metabolism in the hippocampus that leads to spatial memory impairment. Alternatively, chemobrain could be caused by an inflammation-induced increase in cytokine levels that leads to an increase in AChE activity.
- A reduction in synaptic plasticity and, therefore, neuron regeneration and function, is another possible mechanism underlying the effects of chemotherapy on memory and learning.
- A few chemotherapeutic drugs (doxorubicin, cisplatin, and cyclophosphamide) have been found to cause cognitive impairment via mitochondrial dysfunction, but this mechanism has not been studied in the case of other drugs, such as trastuzumab, sunitinib, and methotrexate.
- Chemobrain could potentially be caused by chemotherapy-induced increase in the enzyme TG2, as increased levels of TG2 were found to be associated with memory impairment.
- Aromatase inhibitors and estrogen receptor blockers, which are used in endocrine therapy for cancer, may cause or exacerbate chemobrain, as estrogen is known to play an important role in cognitive function.
- IGF-1 might have beneficial effects against chemotherapy-induced cognitive impairment.

To summarize, while the effects of inflammation and oxidative stress on neurogenesis and their role in chemotherapy-induced cognitive impairment have been widely studied, the chemotherapy-induced cognitive impairment mech-

anisms that involve mitochondrial dysfunction, estrogen dysregulation, and increased transglutaminase 2 are still unclear and need to be investigated in future studies. Investigations into these mechanisms could shed light on preventive and therapeutic strategies against chemobrain.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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