ACCSCIENCE PUBLISHING

Tumor Discovery

REVIEW ARTICLE

Advances in the study of the pathogenesis of cancer-related cognitive impairment

Jiwei Jiang[1,2†], Zhongli Du[3†], Yanli Wang[1,2], Hanping Shi[4], Wenyi Li[1,2], Yuan Zhang[1,2], Mengfan Sun[1,2], Zhimin Bian[5*], and Jun Xu[1,2*]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

[2]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

[3]National Center for Clinical Laboratories, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing Hospital/National Center of Gerontology, Beijing, China

[4]Department of Gastrointestinal Surgery/Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, Beijing, China

[5]Comprehensive Department, National Cancer Center, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China

Abstract

Advances in diagnostic and therapeutic strategies have significantly contributed to an increase in the survival rate of cancer patients. Recently, several studies suggested that cancer patients may exhibit symptoms of cognitive impairment before, during and even many years after the completion of therapies, negatively impacting the quality of life and functional independence of cancer survivors. Clinically, the coexistence of cancer and cognitive impairment reminds scientists of paraneoplastic syndrome, especially limbic encephalitis. However, some cancer patients show symptoms of cognition deterioration after treatment, without any typical psychiatric symptoms, epileptic seizures or positive antineuronal antibodies, suggesting that the relationship between cancer and cognitive deficits is more common than previously anticipated. Most importantly, many aspects of the association between cancer and cognitive impairment remain uncertain. The definitive connection between systemic cancer and central nervous system is yet to be established. Therefore, this review summarizes the current evidence on the potential pathophysiology in these patients with cancer-related cognitive impairment, and reviews the knowledge gaps and the potential counteracting strategies.

Keywords: Cancer; Cognitive impairment; Mechanism; Chemotherapy

†These authors contributed equally to this work.

***Corresponding authors:**
Zhimin Bian
(bzm_0019@sina.com
Jun Xu
(neurojun@126.com)

Citation: Jiang J, Du Z, Wang Y, *et al.*, 2022, Advances in the study of the pathogenesis of cancer-related cognitive impairment. *Tumor Discov,* 1(1): 46.
https://doi.org/10.36922/td.v1i1.46

Received: December 2, 2021
Accepted: March 7, 2022
Published Online: March 22, 2022

1. Introduction

Both cancer and cognitive impairment are diseases showing extremely high incidence and morbidity rates in China. A report published in 2019 by Zhou *et al.*[1] on the population health status of 34 provincial administrative regions in China between 1990 and 2017 indicated that lung and liver cancers ranked among the top five causes of reduction in life expectancy. A recent cross-sectional study that included 46,011 people aged ≥60 years in China showed that the incidence rates of mild cognitive impairment

(MCI) and dementia were as high as 15.5% and 6.0%, respectively[2]. With the continuous improvements in cancer diagnosis and treatment, the mortality rate has declined significantly; the total cancer mortality rate declined by 27% from 1991 to 2016, and those for men and women declined annually by 1.8% and 1.4%, respectively, from 2007 to 2016[3]. Nonetheless, the increase in the life span of cancer patients is accompanied by the increased rates of sequelae and adverse reactions associated with cancer and its treatment. Since 1990s, several studies have confirmed the existence of cancer-related cognitive impairment (CRCI)[4,5]. Cognitive impairment can occur at any stages of cancer, especially during and after chemotherapy, which seriously affects the quality of life and functional independence of patients and heavily burdens their families and the society[6]. At present, CRCI mainly refers to impairment in the cognitive domains of the short-term and working memory, attention, executive functions, and/or processing speed in the patients with systemic cancer following chemotherapy[7]. A nationwide prospective cohort study in China showed that the incidence of cognitive impairment within 6 months after chemotherapy in breast cancer patients was significantly higher than that in age-matched non-cancer patients, which might be associated with anxiety, depression, and reduced cognitive reserve at baseline (pre-chemotherapy) [8]. It is also reported that 30 – 40% of cancer patients have CRCI before treatment, up to 75% may experience cognitive decline during chemotherapy, and 60% may experience cognitive decline after adjuvant therapy[6,9]. This suggests that both cancer and its adjuvant therapy may affect the cognitive function of patients.

Despite evidence of the existence and adverse effects of CRCI, the underlying biological mechanisms remain poorly understood. Moreover, it is unclear whether cognitive decline is caused exclusively by cancer, its treatment, or psychological factors. A systematic review revealed that chemotherapeutic drugs induce the production of superoxide radicals in the peripheral blood that oxidatively modify apolipoprotein A1. Apolipoprotein A1 elevates the pro-inflammatory tumor necrosis factor alpha (TNF-α) levels in the peripheral blood, which induces oxidative stress in brain parenchyma through multiple pathways, thereby inducing apoptosis and affecting the cognitive function[10,11]. It is also known that reactive oxygen species-mediated oxidative stress in the brain tissue is one of the important pathogenic mechanisms of Alzheimer's disease (AD), suggesting that it could be the underlying pathophysiological mechanism of CRCI. However, some studies have demonstrated that the sources of oxidative stress are not identical in these two diseases[12]. It is unclear how systemic cancer establishes a link with the central nervous system (CNS) in the pathological process of eliciting cognitive decline and psychobehavioral abnormalities. Therefore, this article aims to summarize the research results published in the recent decade, reviews, and collates the research progresses on the potential pathogenesis of CRCI, and provides ideas for exploring early intervention and comprehensive management strategies.

2. Direct neurotoxic effects of cancer

2.1. Immunoinflammatory response

Recent studies have shown that the patients with hematologic malignancies and breast cancer experienced cognitive decline prior to receiving any adjuvant therapy[13,14]. Cross-sectional studies revealed that magnetic resonance imaging of patients with breast cancer and several other types of systemic cancers, with or without chemotherapy, showed significant reduction in the cortical surface area or thickness of multiple brain regions[15]. These studies suggested that cancer might have some biological impacts on the cognitive function. The tumor microenvironment (TME) is a complex network comprising tumor cells, tissue stroma, and infiltrating immune cells. All of these can produce inflammatory factors, mainly interleukin (IL)-6, IL-1β, IL-2, IL-8, IL-17, TNF-α, and granulocyte colony-stimulating factor (CSF)[16]. Analysis of the inflammatory markers in 174 newly diagnosed breast cancer patients revealed significant elevated levels of serum IL-1 receptor antagonist as compared to the control participants without cancer (88 cases)[17]. A longitudinal cohort study showed that the levels of 17 cytokines in 75 early-stage breast cancer patients who were on chemotherapy at that time fluctuated over the period of 24 months, and the alterations were associated with specific cognitive domains. This association reveals that prototypical cytokines, such as IL-6, TNF-α, and IL-1β, as well as cytokines from multiple classes may contribute to the inflammatory environment related to cognitive impairment[18]. The cancer itself and its microenvironment can produce inflammatory factors due to local oxidative stressor environmental stimuli. These inflammatory factors enter the brain tissue by directly crossing the blood-brain barrier (BBB) or through the highly permeable capillaries of the circumventricular organs (CVOs)[19]. They activate the glial cells, thus inducing pro-inflammatory signaling cascade or directly interfering with important neuronal circuits[20-22]. Consequently, the homeostasis and cognitive function are affected, thereby establishing a link with the CNS. Moreover, the inflammatory factors activate the macrophages and dendritic cells in and around the blood vessels of the choroid plexus and meninges before entering the brain

parenchyma. This further promotes the polarization of the inflammatory neuroglial cells and ultimately causes pathological, structural, and biochemical changes of the neurons associated with cognitive function[16,23].

2.2. Tumor-derived extracellular vesicles (EV)

EVs are a heterogeneous collection of membrane-bound vesicles released by cells that contain bioactive proteins, nucleic acids, and lipids, and are classified into exosomes and exfoliated microvesicles according to their biological mechanisms[24]. EVs are involved in a variety of normal physiological processes such as coagulation, immune regulation, tissue regeneration, angiogenesis and synaptic plasticity, as well as pathological processes such as neurodegeneration and cancer[25]. With respect to cancer, EVs are involved in various pathological processes related to cancer progression, such as inflammatory response, angiogenesis, lymphogenesis, cell migration and proliferation, immunosuppression, and invasion[26]. It has been established that the initiation, propagation, and resolution of the inflammatory responses to CNS injuries/diseases rely on inflammatory factors and microRNAs (miRNAs), both of which are contained in EVs[27]. Animal experiments have shown that intravenous administration of serum exosomes in the recipient mice from donor mice injected with lipopolysaccharide induced an inflammatory response in the CNS. A series of changes, such as microglial activation, gliosis, increase of pro-inflammatory factors (IL-6 and TNF-α) and production of inflammatory miRNA-155, were observed in the recipient mice[28]. Additionally, a growing line of evidence shows that EVs can serve as novel mediators of cellular communication during normal development and physiological functions of the CNS, as well as normal neuronal regeneration[29]. Under conditions of nutritional deficiency and oxidative stress, neurons can enhance their own viability by internalizing exosomes released from oligodendrocytes[30]. Astrocytes release exosomes containing heat shock protein 70, which also promotes neuronal survival[31]. The uptake of microglia-derived exosomes by neurons induces production of sphingosine and enhances excitatory neurotransmission[32], suggesting that both neurons and supporting cells can participate in cellular communication by secreting exosomes. Tumor-derived EVs may be involved in physiological and pathological processes (synaptic growth and plasticity) by mediating the communication between neurons, thereby affecting brain activity and cognitive function[33]. CNS tumors, such as glioblastoma, remodels the TME by secreting exosomes to induce intracellular transfer of tumor-derived long noncoding RNA SBF2-AS1, or the exosomes secrete pro-permeability factors (e.g., semaphorin 3A) that disrupt the integrity of the vascular endothelial barrier and induce cognitive impairment[34,35]. In systemic cancers, the EVs may affect the cognitive function by activating brain metastasis, which disrupts the BBB integrity, secreting pro-permeability factors to increase BBB permeability and inducing a peripheral blood immune response that triggers brain stress responses[36].

2.3. BBB dysfunction

BBB is a barrier structure formed by endothelial cells interacting with pericytes, astrocytes, neurons, and microglia of the neurovascular unit. BBB not only restricts the entry of potential neurotoxic components and pathogens from the blood into the brain tissue, but also controls the transport of nutrients and energy sources required by the CNS and essential molecules in the blood. In addition, it transports brain metabolites to the periphery to maintain CNS homeostasis and function[37]. Although BBB has a strong regulatory effect, it is also very fragile. Disruption of any component of the structure may induce abnormal neuronal signaling and disrupt the synaptic integrity and BBB permeability, leading to CNS diseases such as ischemic stroke, AD, brain tumors, and systemic inflammation. The most significant and common pathogenesis of these diseases is the effect of neuroinflammatory changes on BBB dysfunction and disease progression[37,38]. As previously discussed, inflammatory factors produced by the cancer cells and TME can enter the CNS by disrupting the BBB integrity or increasing its permeability, subsequently activating glial cells and further initiating the pro-inflammatory signaling cascade, thus affecting the cognitive function. *In vitro* and *in vivo* BBB model studies have shown that EVs secreted by breast cancer cells could enter the brain tissue by transcytosis of the vascular endothelial cells or by disrupting the BBB integrity through CVOs[39]. Dysfunction of the active efflux transport in the BBB can impair the clearance of toxic substances such as β-amyloid (Aβ). The accumulation of Aβ in the brain tissue can promote pathological changes in tau protein and induce or exacerbate cognitive impairment, which is very similar to the pathogenic mechanisms of AD[40]. Furthermore, persistent angiogenesis and immunosuppression are the typical features of cancer, and pathological angiogenesis is associated with abnormal blood flow and dysfunction of the BBB[41]. Angiopoietin-2 is an early vascular marker in glioblastoma multiforme. In addition to regulating vascular development, maturation, and immediate vascular response, its overexpression can lead to pericyte defects, disruption of endothelial cell integrity, and interference with the BBB function[42]. Thus, immune inflammatory factors and EVs released by cancer cells

can lead to abnormal angiogenesis and other pathogenic changes that can disrupt the integrity and physiological function of the BBB. BBB dysfunction can also exacerbate the pathological protein deposition in the brain tissue and aggravate cognitive impairment.

3. Antitumor therapy-related neuronal damage

3.1. Chemotherapy

The adverse effects of cancer chemotherapies often manifest as peripheral neuropathy, ototoxicity, pulmonary fibrosis, as well as abnormalities in hepatic and renal functions[43]. Recently, there have been several reports on chemotherapy-induced cognitive impairment (CICI), and some scholars refer this impairment of attention, memory, learning and language function, and other cognitive domains to as "chemo brain" or "chemo fog"[44]. CICI can occur both during or several years after chemotherapy[6,45]. A nationwide longitudinal cohort study in China showed that patients with stage I-IIIC breast cancer exhibit significant impairment in multiple cognitive domains, including memory, attention, and executive functions, within 6 months after chemotherapy[46]. There is a dose-response relationship between chemotherapy drugs and cognitive function. Collins *et al.*[47] performed neuropsychological tests in 60 postoperative patients with early-stage breast cancer before chemotherapy and at the end of each chemotherapy cycle. They found that the cognitive function of the patients undergoing chemotherapy declined progressively during the course (i.e., as the doses of chemotherapy drugs increased). Although there are a variety of chemotherapy drugs, the cognitive and neurological effects of only a selection of drugs have been reported, mainly alkylating agents (cyclophosphamide), antimetabolites (methotrexate and 5-fluorouracil), cytotoxic antibiotics (doxorubicin), antimicrotubule agents (paclitaxel and docetaxel), monoclonal antibodies (trastuzumab and rituximab), and immune checkpoint inhibitors[48]. The specific etiology and pathogenesis of CICI remain unclear. Based on the available research evidence, the hypothesized pathogenesis involves multiple dimensions, mainly direct neurotoxic effects of drugs, immune dysfunction, oxidative stress response, and altered cerebral blood flow[48,49]. The transport of cisplatin, a commonly used chemotherapy agent for lung cancer, across the BBB is mediated by the copper uptake protein copper transporter 1, which, in turn, induces brain network abnormalities, impaired glucose metabolism, and cognitive impairment[50]. Animal studies have shown that systemically administered chemotherapy drugs, such as cisplatin and carmustine, act on the CNS progenitor cells, whose proliferation produces oligodendrocytes that are important for myelin formation and neuroplasticity; the myelinated axons constitute the white matter of the brain[47,51]. Furthermore, 5-fluorouracil is associated with reduced myelination of the corpus callosum and dysregulated expression of oligodendrocyte transcription factor 2 in rats[52]. The number of oligodendrocytes and their progenitor cells in the white matter, volume of the corpus callosum, and myelin basic protein decreased significantly in a rat cancer model after 6 and 16 months of treatment with methotrexate[53]. This suggests that the toxic effects of chemotherapy agents are associated with myelin formation and white matter abnormalities in the brain regions related to cognition. In addition, the toxic effects of these drugs may also lead to increased necrosis and apoptosis and reduced proliferation of the hippocampal neurons, interfering with the neurogenesis in the hippocampus and other regions, which in turn affects learning and memory[54,55]. Moreover, chemotherapy drugs promote the release of inflammatory factors in the peripheral blood, which subsequently cross the BBB or induce the release of inflammatory factors in the CNS. This causes cognitive impairment by mediating neuroimmune inflammatory responses and affecting epigenetic modifications. Doxorubicin can increase the levels of inflammatory factors and TNF-α in the peripheral blood; the latter crosses the BBB through receptor-mediated endocytosis and accumulates in the brain tissue, causing oxidative and nitrosative damage to important biomolecules, mitochondrial dysfunction, and neuronal apoptosis[56,57]. On the other hand, chemotherapy drugs can activate the microglia to release pro-inflammatory factors, such as IL-6 and TNF-α, or alter the interaction between astrocytes and oligodendrocytes, inhibit hippocampal neurogenesis and myelin plasticity in white matter, and interfere with neurotransmission and axon formation, thus resulting in cognitive impairment[58-60]. Animal experiments showed that the levels of inflammatory mediators, such as IL-1β, TNF-α, and cyclooxygenase-2, increased significantly and the level of the anti-inflammatory factor IL-10 decreased in rats 4 weeks after 5-fluorouracil injection[52]. Lyon *et al.*[61] suggested that inflammatory factors might induce DNA methylation mediated by protein enhancer of zeste 2 (an important DNA repair enzyme) and chromosomal instability (telomere shortening), causing cell death or abnormal gene expression, ultimately leading to CICI. Oxidative stress caused by an imbalance between the generation of reactive oxygen species (including free radicals and peroxides) and the biological antioxidant defense system is considered another potential pathogenic mechanism of CICI. Animal experiments showed that doxorubicin treatment increased the sensitivity of calcium-mediated brain mitochondrial permeability transition pore in rats and the mitochondrial membrane permeability,

which, in turn, led to mitochondrial swelling and rupture and induced oxidative stress in the brain tissue[62]. Methotrexate increases the level of malondialdehyde in rat cerebellum by interacting with enzymes in the folate metabolic pathway, thereby inducing oxidative stress[63]. Chemotherapy-activated oxidative stress (accumulation of reactive oxygen species) induces mitochondrial DNA mutations and reduces the antioxidant capacity of CNS, resulting in cognitive impairment[64]. In addition, it damages the cerebral vasculature by exacerbating thrombosis and interfering with cerebral small vessel perfusion or activating transcription factor 3-mediated lipotoxic brain microvascular injury, resulting in cognitive impairment by a mechanism similar to that of vascular dementia[65].

3.2. Other adjuvant therapies

In addition to chemotherapy, hormonal therapy, or endocrine therapy, targeted therapies such as those with anti-angiogenic agents, and immunotherapy can also cause cognitive impairment. Endocrine therapies for breast cancer include selective estrogen receptor modulators (e.g., tamoxifen) and aromatase inhibitors (e.g., letrozole). Tamoxifen treatment can affect specific cognitive domains such as memory, language function, executive functions, and processing speed in patients with breast cancer[66]. Cell line models showed that tamoxifen could not only affect the neuronal activity by modulating exocytosis and catecholamine storage in vesicles but also acts on voltage-gated potassium channels to interfere with the secretion of neurotransmitters, thereby affecting cognitive function[67]. Spatial working memory impairment was observed in primates after letrozole administration, which might be related to increased estradiol levels and reduced neuronal excitability in the hippocampus after drug administration[68]. A prospective study showed that approximately 31.03% (18/58) of 75 patients with metastatic renal cell carcinoma receiving targeted therapy suffered from the impairments in information processing and working memory unrelated to fatigue[69]. A cross-sectional study by Mulder *et al.*[70] compared the cognitive functions of patients with metastatic renal cell carcinoma or gastrointestinal stromal tumors receiving targeted therapy with vascular endothelial growth factor receptor (VEGFR) inhibitors (sunitinib or sorafenib), patients with untreated metastatic renal cell carcinoma, and healthy controls. They found that the cognitive functions, particularly learning, memory, and executive functions, were significantly reduced in cancer patients. Moreover, these cognitive impairments were more severe in the cancer patients receiving anti-angiogenic therapy than in those receiving others. Targeted anti-angiogenic agents, such as sunitinib, may induce cognitive impairment by blocking VEGFR2 signaling, autophagy, and overactive apoptosis[71].

Immunotherapies mainly comprising immune checkpoint inhibitors and chimeric antigen receptor T-cell (CAR-T) therapy are the most promising approaches for cancer treatment to date. At present, the evidence of cognitive impairment caused by antitumor drugs is mostly focused on chemotherapy and targeted therapy, and there is still a lack of basic and clinical studies on the relationship between immunotherapy and cognitive function[72,73]. This may be attributed to the frequent use of novel antitumor therapies in combination with other therapies, small sample sizes for clinical studies, and difficulty in excluding the interference of chemotherapy or radiotherapy with cognitive function[74]. A prospective multicenter phase II clinical trial showed that patients with refractory large B-cell lymphoma treated with CAR-T therapy might develop neurological symptoms, such as delirium, cognitive impairment and encephalopathy, myelosuppression, and cytokine release syndrome (CRS)[75]. CAR-T therapy leads to CRS by activating T lymphocytes and recruiting neighboring immune cells to release a range of inflammatory factors and CSFs, thus affecting multiple organs and systems including the CNS[76,77]. Radiotherapy is a crucial treatment modality for metastatic tumors as well as head and neck malignancies. It has been established that radiotherapy parameters have a negative impact on the cognitive function, including total dose, dose per fraction, and treated volume[78]. A cohort study by McDowell *et al.*[79] showed that a moderate to high proportion of patients with nasopharyngeal carcinoma treated with intensive radiotherapy developed cognitive impairment and psychobehavioral abnormalities, particularly apathy, disinhibition, and executive dysfunction. A cross-sectional study of 78 patients with primary brain tumors treated with radiotherapy showed that hippocampal tissues were susceptible to radiotherapy, and high-dose radiation to the left hippocampus led to impaired verbal learning and memory[80]. A systematic review suggested that acute radiotherapy could synergistically alter the signaling microenvironment in progenitor cell niches in the brain and hippocampus by triggering CNS inflammation, damaging neuronal lineages and glial cells and their progenitors, and disrupting the integrity of the supporting structures, thereby causing progressive neuronal loss and cognitive impairment[81].

4. Common risk factors for cancer and cognitive impairment

Aging is a common risk factor for many diseases, including cancer and neurodegenerative disorders. It is believed that cumulative adverse reactions lead to genomic instability, mitochondrial dysfunction, DNA damage, or impaired DNA repair process[82]. Cancer and neurodegeneration with cognitive impairment may share common signal

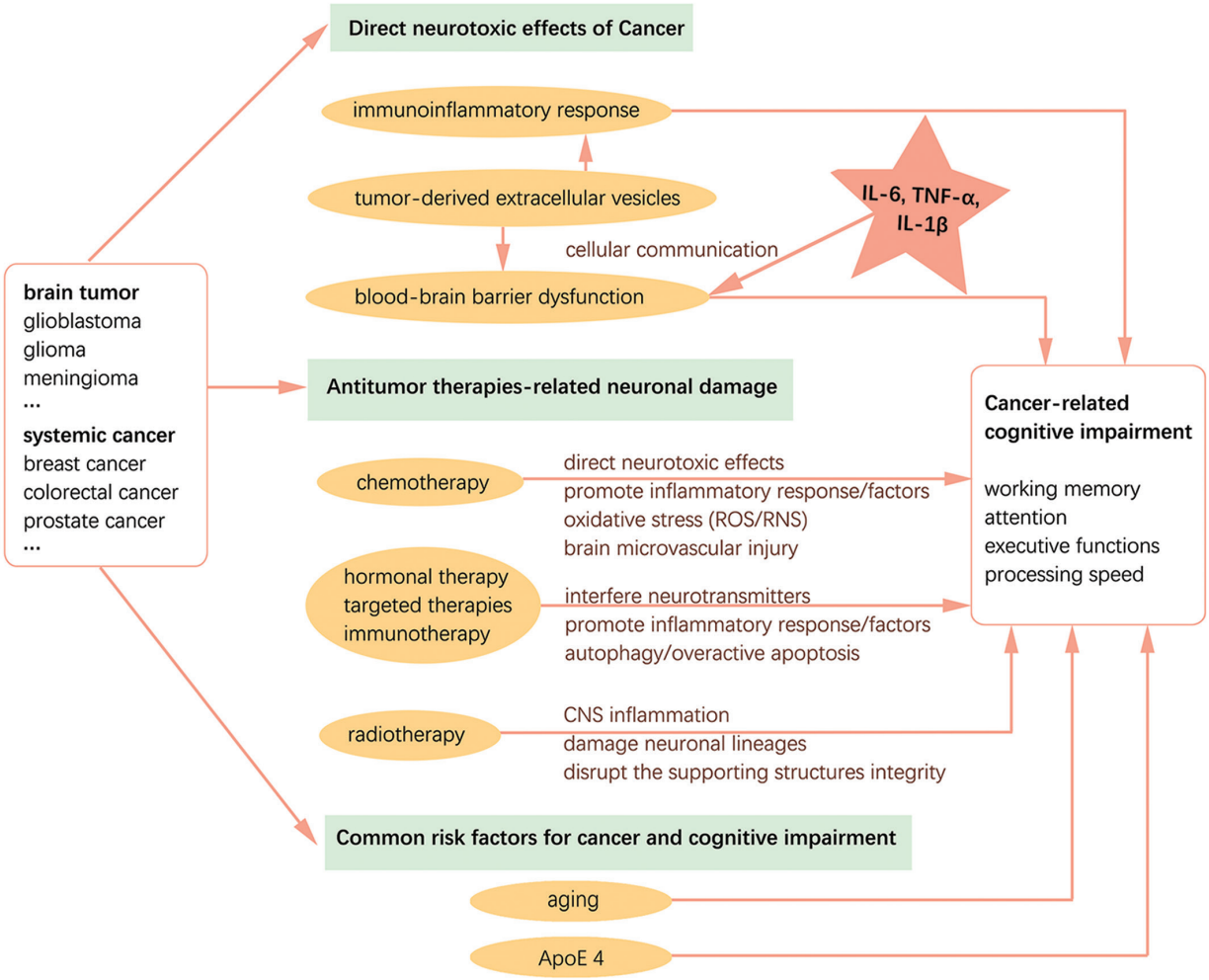

Figure 1. Candidate mechanisms and their interrelations between cancer and cognitive impairment.

transduction pathways that regulate cell survival and death. A common tumor suppressor gene, *p53*, whose mutation or dysfunction can damage the cellular genome, plays an important role in the development and progression of cancer. Systematic reviews have hypothesized that in aging neurons, dysfunction of proteins that regulate the cell cycle and apoptosis, such as *p53*, may affect the neuronal plasticity and function, revealing a bridging role of *p53* gene in the progression of cancer and neurodegeneration[83,84]. There is evidence that DNA methylation and histone acetylation play important roles in the activation and suppression of cancer genes, and abnormalities of these epigenetic modifications are associated with the progression of neurodegeneration[85]. Apolipoprotein E (*ApoE*) plays a role in neuronal repair and plasticity after injury, and its ε*4* allele (*ApoE* ε*4*) is closely associated with AD-related cognitive impairment and craniocerebral trauma[86]. It was found that the cancer patients undergoing chemotherapy with at least one *ApoE* ε*4* allele had significantly lower scores in all cognitive domains than cancer survivors who did not have *ApoE* ε*4* allele[87]. Furthermore, the anti-inflammatory property of *ApoE* and its involvement in proper neurogenesis can be affected by oxidative stress and inflammatory response induced by chemotherapy drugs[88]. Thus, CRCI has a complex pathogenetic mechanism in which the immune system, genetic factors, host behavior, and psychosocial state interact with each other as reciprocal causation (Figure 1). Further clinical studies and animal models are warranted to fully elucidate its pathogenesis.

5. Conclusion

Cognitive impairment in cancer patients is more common than that recognized previously. CRCI may occur before, during, or even more than 10 years after cancer treatment, primarily involving four cognitive domains,

that is, executive functions, processing speed, memory, and attention. At present, although the etiology and pathogenesis of CRCI are not well understood, they may be related to the biological effects of cancer, adverse effects of cancer treatment, or common potential risk factors for both cancer and cognitive impairment. Further clinical and basic research is warranted in the future to elucidate the actual mechanisms of CRCI to develop detailed diagnosis and management strategies for such patients.

Acknowledgments

None.

Funding

This study was supported by the National Natural Science Foundation of China (81870821 and 82071187) and Beijing Youth Talent Team Support Program (2018000021223TD08).

Conflict of interest

No conflict of interest was reported by all authors.

Author contributions

Conceptualization: Jiwei Jiang, Zhongli Du, Zhimin Bian, Jun Xu

Data curation: Yanli Wang

Funding acquisition: Zhimin Bian, Jun Xu

Supervision: Zhimin Bian, Jun Xu

Writing – original draft: Jiwei Jiang, Zhongli Du

Writing – review & editing: Jiwei Jiang, Zhongli Du, Yanli Wang, Hanping Shi, Wenyi Li, Yuan Zhang, Mengfan Sun, Zhimin Bian, Jun Xu

References

1. Zhou M, Wang H, Zeng X, *et al*., 2019, Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet*, 394: 1145–1158.

   https://doi.org/10.1016/S0140-6736(19)30427-1

2. Jia L, Du Y, Chu L, Zhang Z, Li F, Lyu D, *et al*., 2020, Prevalence, risk factors, and management of dementia and mild cognitive impairment in adults aged 60 years or older in China: A cross-sectional study. *Lancet Public Health*, 5: e661–e671.

   https://doi.org/10.1016/S2468-2667(20)30185-7

3. Siegel RL, Miller KD, Jemal A, 2019, Cancer statistics, 2019. *CA Cancer J Clin*, 69: 7–34.

   https://doi.org/10.3322/caac.21551

4. Ren X, Boriero D, Chaiswing L, *et al*., 2019. Plausible biochemical mechanisms of chemotherapy-induced cognitive impairment ("chemobrain"), a condition that significantly impairs the quality of life of many cancer survivors. *Biochim Biophys Acta Mol Basis Dis*, 1865(6): 1088–1097.

   https://doi.org/10.1016/j.bbadis.2019.02.007

5. Ahles TA, Root JC, 2018, Cognitive effects of cancer and cancer treatments. *Annu Rev Clin Psychol*, 14: 425–451.

   https://doi.org/10.1146/annurev-clinpsy-050817-084903

6. Wefel JS, Kesler SR, Noll KR, *et al*., 2015, Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. *CA Cancer J Clin*, 65: 123–138.

   https://doi.org/10.3322/caac.21258

7. Lange M, Joly F, Vardy J, *et al*., 2019, Cancer-related cognitive impairment: An update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol*, 30(12): 1925–1940.

   https://doi.org/10.1093/annonc/mdz410

8. Janelsins MC, Heckler CE, Peppone LJ, *et al*., 2017, Cognitive complaints in survivors of breast cancer after chemotherapy compared with age-matched controls: An analysis from a nationwide, multicenter, prospective longitudinal study. *J Clin Oncol*, 35(5): 506–514.

   https://doi.org/10.1200/jco.2016.68.5826

9. Janelsins MC, Kesler SR, Ahles TA, *et al*., 2014, Prevalence, mechanisms, and management of cancer-related cognitive impairment. *Int Rev Psychiatry*, 26(1): 102–113.

   https://doi.org/10.3109/09540261.2013.864260

10. Rummel NG, Chaiswing L, Bondada S, *et al*., 2021, Chemotherapy-induced cognitive impairment: focus on the intersection of oxidative stress and TNFα. *Cell Mol Life Sci*, 78(19–20): 6533–6540.

    https://doi.org/10.1007/s00018-021-03925-4

11. Ren X, Keeney JT, Miriyala S, *et al*., 2019, The triangle of death of neurons: oxidative damage, mitochondrial dysfunction, and loss of choline-containing biomolecules in brains of mice treated with doxorubicin: Advanced insights into mechanisms of chemotherapy induced cognitive impairment ("chemobrain") involving TNF-α. *Free Radic Biol Med*, 134: 1–8.

    https://doi.org/10.1016/j.freeradbiomed.2018.12.029

12. Tönnies E, Trushina E, 2017, Oxidative stress, synaptic dysfunction, and Alzheimer's disease. *J Alzheimers Dis*, 57: 1105–1121.

    https://doi.org/10.3233/jad-161088

13. Williams AM, van Wijngaarden E, Seplaki CL, *et al*., 2020, Cognitive function in patients with chronic lymphocytic

leukemia: A cross-sectional study examining effects of disease and treatment. *Leuk Lymphoma*, 61(7): 1627–1635.

https://doi.org/10.1080/10428194.2020.1728748

14. Kaiser J, Dietrich J, Amiri M, *et al*., 2020, Cognitive performance and psychological distress in breast cancer patients at disease onset. *Front Psychol*, 10: 2584.

https://doi.org/10.3389/fpsyg.2019.02584

15. Shiroishi MS, Gupta V, Bigjahan B, *et al*., 2017, Brain cortical structural differences between non-central nervous system cancer patients treated with and without chemotherapy compared to non-cancer controls: A cross-sectional pilot MRI study using clinically-indicated scans. *Proc SPIE Int Soc Opt Eng*, 10572: 105720G.

https://doi.org/10.1117/12.2285971

16. Olson B, Marks DL, 2019, Pretreatment cancer-related cognitive impairment-mechanisms and outlook. *Cancers* (*Basel*), 11(5): 687.

https://doi.org/10.3390/cancers11050687

17. Patel SK, Wong AL, Wong FL, *et al*., 2015, Inflammatory biomarkers, comorbidity, and neurocognition in women with newly diagnosed breast cancer. *J Natl Cancer Inst*, 107(8): djv131.

https://doi.org/10.1093/jnci/djv131

18. Lyon DE, Cohen R, Chen H, *et al*., 2016, Relationship of systemic cytokine concentrations to cognitive function over two years in women with early stage breast cancer. *J Neuroimmunol*, 301: 74–82.

https://doi.org/10.1016/j.jneuroim.2016.11.002

19. Wardill HR, Mander KA, Van Sebille YZ, *et al*., 2016, Cytokine-mediated blood brain barrier disruption as a conduit for cancer/chemotherapy-associated neurotoxicity and cognitive dysfunction. *Int J Cancer*, 139(12): 2635–2645.

https://doi.org/10.1002/ijc.30252

20. Santos JC, Pyter LM, 2018, Neuroimmunology of behavioral comorbidities associated with cancer and cancer treatments. *Front Immunol*, 9: 1195.

https://doi.org/10.3389/fimmu.2018.01195

21. Kaur D, Sharma V, Deshmukh R, 2019, Activation of microglia and astrocytes: a roadway to neuroinflammation and Alzheimer's disease. *Inflammopharmacology*, 27(4): 663–677.

https://doi.org/10.1007/s10787-019-00580-x

22. Capuron L, Miller AH, 2011, Immune system to brain signaling: neuropsychopharmacological implications. *Pharmacol Ther*, 130(2): 226–238.

https://doi.org/10.1016/j.pharmthera.2011.01.014

23. Fischer HG, Reichmann G, 2001, Brain dendritic cells and macrophages/microglia in central nervous system inflammation. *J Immunol*, 166(4): 2717–2726.

https://doi.org/10.4049/jimmunol.166.4.2717

24. Clancy J, D'Souza-Schorey C, 2018, Extracellular vesicles in cancer: purpose and promise. *Cancer J*, 24(2): 65–69.

https://doi.org/10.1097/ppo.0000000000000306

25. Xu R, Rai A, Chen M, *et al*., 2018, Extracellular vesicles in cancer: Implications for future improvements in cancer care. *Nat Rev Clin Oncol*, 15(10): 617–638.

https://doi.org/10.1038/s41571-018-0036-9

26. Kok VC, Yu CC, 202, Cancer-derived exosomes: Their role in cancer biology and biomarker development. *Int J Nanomed*, 15: 8019–8036.

https://doi.org/10.2147/IJN.S272378

27. Delpech JC, Herron S, Botros MB, *et al*., 2019, Neuroimmune crosstalk through extracellular vesicles in health and disease. *Trends Neurosci*, 42(5): 361–372.

https://doi.org/10.1016/j.tins.2019.02.007

28. Li JJ, Wang B, Kodali MC, *et al*., 2018, *In vivo* evidence for the contribution of peripheral circulating inflammatory exosomes to neuroinflammation. *J Neuroinflammation*, 15(1): 8.

https://doi.org/10.1186/s12974-017-1038-8

29. Pascual M, Ibáñez F, Guerri C, 2020, Exosomes as mediators of neuron-glia communication in neuroinflammation. *Neural Regen Res*, 15(5): 796–801.

https://doi.org/10.4103/1673-5374.268893

30. Frühbeis C, Kuo-Elsner WP, Müller C, *et al*., 2002. Oligodendrocytes support axonal transport and maintenance via exosome secretion. *PLoS Biol*, 18(12): e3000621.

https://doi.org/10.1371/journal.pbio.3000621

31. Gharbi T, Zhang Z, Yang GY, 2020, The function of astrocyte mediated extracellular vesicles in central nervous system diseases. *Front Cell Dev Biol*, 8: 568889.

https://doi.org/10.3389/fcell.2020.568889

32. Antonucci F, Turola E, Riganti L, *et al*., 2012, Microvesicles released from microglia stimulate synaptic activity via enhanced sphingolipid metabolism. *EMBO J*, 31(5): 1231–1240.

https://doi.org/10.1038/emboj.2011.489

33. Zhang G, Yang P, 2018, A novel cell-cell communication mechanism in the nervous system: exosomes. *J Neurosci Res*, 96(1): 45–52.

https://doi.org/10.1002/jnr.24113

34. Treps L, Edmond S, Harford-Wright E, *et al*., 2016, Extracellular vesicle-transported Semaphorin3A promotes vascular permeability in glioblastoma. *Oncogene*, 35(20): 2615–2623.

https://doi.org/10.1038/onc.2015.317

35. Zhang Z, Yin J, Lu C, *et al.*, 2019, Exosomal transfer of long non-coding RNA SBF2-AS1 enhances chemoresistance to temozolomide in glioblastoma. *J Exp Clin Cancer Res*, 38(1): 166.

https://doi.org/10.1186/s13046-019-1139-6

36. Koh YQ, Tan CJ, Toh YL, *et al.*, 2020, Role of exosomes in cancer-related cognitive impairment. *Int J Mol Sci*, 21(8):2755.

https://doi.org/10.3390/ijms21082755

37. Sweeney MD, Zhao Z, Montagne A, *et al.*, 2019, Blood-brain barrier: from physiology to disease and back. *Physiol Rev*, 99(1): 21–78.

https://doi.org/10.1152/physrev.00050.2017

38. Liebner S, Dijkhuizen RM, Reiss Y, *et al.*, 2018, Functional morphology of the blood-brain barrier in health and disease. *Acta Neuropathol*, 135(3): 311–336.

https://doi.org/10.1007/s00401-018-1815-1

39. Morad G, Carman CV, Hagedorn EJ, *et al.*, 2019, Tumor-derived extracellular vesicles breach the intact blood-brain barrier via transcytosis. *ACS Nano*, 13(12): 13853–13865.

https://doi.org/10.1021/acsnano.9b04397

40. Sweeney MD, Sagare AP, Zlokovic BV, 2018, Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorder. *Nat Rev Neurol*, 14(3): 133–150.

https://doi.org/10.1038/nrneurol.2017.188

41. Hanahan D, Weinberg RA, 2011, Hallmarks of cancer: The next generation. *Cell*, 144(5): 646–674.

https://doi.org/10.1016/j.cell.2011.02.013

42. Saharinen P, Eklund L, Alitalo K, 2017, Therapeutic targeting of the angiopoietin-TIE pathway. *Nat Rev Drug Discov*, 16(9): 635–661.

43. Zajączkowska R, Kocot-Kępska M, Leppert W, *et al.*, 2019, Mechanisms of chemotherapy-induced peripheral neuropathy. *Int J Mol Sci*, 20(6): 1451.

https://doi.org/10.3390/ijms20061451

44. Vitali M, Ripamonti CI, Roila F, *et al.*, 2017. Cognitive impairment and chemotherapy: A brief overview. *Crit Rev Oncol Hematol*, 118: 7–14.

https://doi.org/10.1016/j.critrevonc.2017.08.001

45. de Ruiter MB, Reneman L, Boogerd W, *et al.*, 2011, Cerebral hyporesponsiveness and cognitive impairment 10 years after chemotherapy for breast cancer. *Hum Brain Mapp*, 32(8): 1206–1219.

https://doi.org/10.1002/hbm.21102

46. Janelsins MC, Heckler CE, Peppone LJ, *et al.*, 2018, Longitudinal trajectory and characterization of cancer-related cognitive impairment in a nationwide cohort study. *J Clin Oncol*, 36(32): JCO2018786624.

https://doi.org/10.1200/jco.2018.78.6624

47. Collins B, MacKenzie J, Tasca GA, *et al.*, 2013, Cognitive effects of chemotherapy in breast cancer patients: A dose-response study. *Psychooncology*, 22(7): 1517–1527.

https://doi.org/10.1002/pon.3163

48. Mounier NM, Abdel-Maged AE, Wahdan SA, *et al.*, 2020, Chemotherapy-induced cognitive impairment (CICI): An overview of etiology and pathogenesis. *Life Sci*, 258: 118071.

https://doi.org/10.1016/j.lfs.2020.118071

49. Bagnall-Moreau C, Chaudhry S, Salas-Ramirez K, *et al.*, 2019, Chemotherapy-induced cognitive impairment is associated with increased inflammation and oxidative damage in the hippocampus. *Mol Neurobiol*, 56(10): 7159–7172.

https://doi.org/10.1007/s12035-019-1589-z

50. Michalak S, Rybacka-Mossakowska J, Ambrosius W, *et al.*, 2016, The markers of glutamate metabolism in peripheral blood mononuclear cells and neurological complications in lung cancer patients. *Dis Markers*, 2016: 2895972.

https://doi.org/10.1155/2016/2895972

51. Gibson EM, Purger D, Mount CW, *et al.*, 2014, Neuronal activity promotes oligodendrogenesis and adaptive myelination in the mammalian brain. *Science*, 344(6183): 1252304.

https://doi.org/10.1126/science.1252304

52. Briones TL, Woods J, 2014, Dysregulation in myelination mediated by persistent neuroinflammation: Possible mechanisms in chemotherapy-related cognitive impairment. *Brain Behav Immun*, 35: 23–32.

https://doi.org/10.1016/j.bbi.2013.07.175

53. Berlin C, Lange K, Lekaye HC, *et al.*, 2020, Long-term clinically relevant rodent model of methotrexate-induced cognitive impairment. *Neuro Oncol*, 22(8): 1126-1137.

https://doi.org/10.1093/neuonc/noaa086

54. Sirichoat A, Krutsri S, Suwannakot K, *et al.*, 2019, Melatonin protects against methotrexate-induced memory deficit and hippocampal neurogenesis impairment in a rat model. *Biochem Pharmacol*, 163: 225–233.

55. Sirichoat A, Suwannakot K, Chaisawang P, *et al.*, 2020, Melatonin attenuates 5-fluorouracil-induced spatial memory and hippocampal neurogenesis impairment in adult rats. *Life Sci*, 248: 117468.

https://doi.org/10.1016/j.lfs.2020.117468

56. El-Agamy SE, Abdel-Aziz AK, Wahdan S, *et al.*, 2018, Astaxanthin ameliorates doxorubicin-induced cognitive impairment (chemobrain) in experimental rat model: Impact on oxidative, inflammatory, and apoptotic machineries. *Mol Neurobiol*, 55(7): 5727–5740.

https://doi.org/10.1007/s12035-017-0797-7

57. Keeney JT, Miriyala S, Noel T, *et al.*, 2015, Superoxide

induces protein oxidation in plasma and TNF-α elevation in macrophage culture: Insights into mechanisms of neurotoxicity following doxorubicin chemotherapy. *Cancer Lett*, 367(2): 157–161.

https://doi.org/10.1016/j.canlet.2015.07.023

58. Lv L, Mao S, Dong H, *et al*., 2020, Pathogenesis, assessments, and management of chemotherapy-related cognitive impairment (CRCI): An updated literature review. *J Oncol*, 2020: 3942439.

https://doi.org/10.1155/2020/3942439

59. Ren X, St Clair DK, Butterfield DA, 2017, Dysregulation of cytokine mediated chemotherapy induced cognitive impairment. *Pharmacol Res*, 117: 267–273.

https://doi.org/10.1016/j.phrs.2017.01.001

60. Gibson EM, Monje M, 2019, Emerging mechanistic underpinnings and therapeutic targets for chemotherapy-related cognitive impairment. *Curr Opin Oncol*, 31(6): 531–539.

https://doi.org/10.1097/cco.0000000000000578

61. Lyon D, Elmore L, Aboalela N, *et al*., 2014, Potential epigenetic mechanism(s) associated with the persistence of psychoneurological symptoms in women receiving chemotherapy for breast cancer: A hypothesis. *Biol Res Nurs*, 16(2): 160-174.

62. Cardoso S, Santos RX, Carvalho C, *et al*., 2008, Doxorubicin increases the susceptibility of brain mitochondria to $Ca^{(2+)}$-induced permeability transition and oxidative damage. *Free Radic Biol Med*, 45(10): 1395–1402.

63. Uzar E, Koyuncuoglu HR, Uz E, *et al*., 2006, The activities of antioxidant enzymes and the level of malondialdehyde in cerebellum of rats subjected to methotrexate: Protective effect of caffeic acid phenethyl ester. *Mol Cell Biochem*, 291(1-2): 63–68.

https://doi.org/10.1007/s11010-006-9196-5

64. Cauli O, 2021, Oxidative stress and cognitive alterations induced by cancer chemotherapy drugs: A scoping review. *Antioxidants* (*Basel*), 10(7): 1116.

https://doi.org/10.3390/antiox10071116

65. Nyunt T, Britton M, Wanichthanarak K, *et al*., 2019, Mitochondrial oxidative stress-induced transcript variants of ATF3 mediate lipotoxic brain microvascular injury. *Free Radic Biol Med*, 143: 25–46.

https://doi.org/10.1016/j.freeradbiomed.2019.07.024

66. Jebahi F, Sharma S, Bloss JE, *et al*., 2021, Effects of tamoxifen on cognition and language in women with breast cancer: A systematic search and a scoping review. *Psychooncology*, 30(8): 1262–1277.

https://doi.org/10.1002/pon.5696

67. Taleat Z, Larsson A, Ewing AG, 2019, Anticancer drug tamoxifen affects catecholamine transmitter release and storage from single cells. *ACS Chem Neurosci*, 10(4): 2060–2069.

https://doi.org/10.1021/acschemneuro.8b00714

68. Gervais NJ, Remage-Healey L, Starrett JR, *et al*., 2019, Adverse effects of aromatase inhibition on the brain and behavior in a nonhuman primate. *J Neurosci*, 39(5): 918–928.

https://doi.org/10.1523/jneurosci.0353-18.2018

69. Joly F, Heutte N, Duclos B, *et al*., 2016, Prospective evaluation of the impact of antiangiogenic treatment on cognitive functions in metastatic renal cancer. *Eur Urol Focus*, 2(6): 642–649.

https://doi.org/10.1016/j.euf.2016.04.009

70. Mulder SF, Bertens D, Desar IM, *et al*., 2014, Impairment of cognitive functioning during sunitinib or sorafenib treatment in cancer patients: A cross sectional study. *BMC Cancer*, 14: 219.

https://doi.org/10.1186/1471-2407-14-219

71. Abdel-Aziz AK, Mantawy EM, Said RS, *et al*., 2016, The tyrosine kinase inhibitor, sunitinib malate, induces cognitive impairment *in vivo* via dysregulating VEGFR signaling, apoptotic and autophagic machineries. *Exp Neurol*, 283(Pt A): 129–141.

72. Joly F, Castel H, Tron L, *et al*., 2020, Potential effect of immunotherapy agents on cognitive function in cancer patients. *J Natl Cancer Inst*, 112(2): 123–127.

https://doi.org/10.1093/jnci/djz168

73. Greenbaum U, Kebriaei P, Srour SA, *et al*., 2021, Chimeric antigen receptor T-cell therapy toxicities. *Br J Clin Pharmacol*, 87(6): 2414–2424.

https://doi.org/10.1111/bcp.14403

74. Cuzzubbo S, Belin C, Chouahnia K, *et al*., 2018, Assessing cognitive function in patients treated with immune checkpoint inhibitors: A feasibility study. *Psychooncology*, 27(7): 1861–1864.

https://doi.org/10.1002/pon.4725

75. Neelapu SS, Locke FL, Bartlett NL, *et al*., 2017, Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. *N Engl J Med*, 377(26): 2531–2544.

https://doi.org/10.1056/nejmoa1707447

76. Chen H, Wang F, Zhang P, *et al*., 2019, Management of cytokine release syndrome related to CAR-T cell therapy. *Front Med*, 13(5): 610–617.

https://doi.org/10.1007/s11684-019-0714-8

77. Santomasso BD, Park JH, Salloum D, *et al*., 2018, Clinical and biologic correlates of neurotoxicity associated with CAR T cell therapy in patients with B-cell acute lymphoblastic leukemia. *Cancer Discov*, 8(8): 958–971.

https://doi.org/10.1158/2159-8290.cd-17-1319

78. Pazzaglia S, Briganti G, Mancuso M, *et al*., 2020,

Neurocognitive decline following radiotherapy: Mechanisms and therapeutic implications. *Cancers* (*Basel*), 12: 146.

https://doi.org/10.3390/cancers12010146

79. McDowell LJ, Ringash J, Xu W, *et al*., 2019, A cross sectional study in cognitive and neurobehavioral impairment in long-term nasopharyngeal cancer survivors treated with intensity-modulated radiotherapy. *Radiother Oncol*, 131: 179–185.

https://doi.org/10.1016/j.radonc.2018.09.012

80. Haldbo-Classen L, Amidi A, Lukacova S, *et al*., 2020, Cognitive impairment following radiation to hippocampus and other brain structures in adults with primary brain tumours. *Radiother Oncol*, 148: 1–7.

https://doi.org/10.1016/j.radonc.2020.03.023

81. Makale MT, McDonald CR, Hattangadi-Gluth JA, *et al*., 2017, Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. *Nat Rev Neurol*, 13(1): 52–64.

https://doi.org/10.1038/nrneurol.2016.185

82. McHugh D, Gil J, 2018, Senescence and aging: causes, consequences, and therapeutic avenues. *J Cell Biol*, 217(1): 65–77.

https://doi.org/10.1083/jcb.201708092

83. Seo J, Park M, 2020, Molecular crosstalk between cancer and neurodegenerative diseases. *Cell Mol Life Sci*, 77(14): 2659–2680.

https://doi.org/10.1007/s00018-019-03428-3

84. Lanni C, Masi M, Racchi M, *et al*., 2021, Cancer and Alzheimer's disease inverse relationship: an age-associated diverging derailment of shared pathways. *Mol Psychiatry*, 26(1): 280–295.

https://doi.org/10.1038/s41380-020-0760-2

85. Nebbioso A, Tambaro FP, Dell'Aversana C, *et al*., 2018, Cancer epigenetics: moving forward. *PLoS Genet*, 14(6): e1007362.

https://doi.org/10.1371/journal.pgen.1007362

86. Rebeck GW, 2017, The role of APOE on lipid homeostasis and inflammation in normal brains. *J Lipid Res*, 58(8): 1493–1499.

https://doi.org/10.1194/jlr.R075408

87. Ahles TA, Saykin AJ, Noll WW, *et al*., 2003, The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncology*, 12(6): 612–619.

https://doi.org/10.1002/pon.742

88. Fernandez HR, Varma A, Flowers SA, *et al*., 2020, Cancer chemotherapy related cognitive impairment and the impact of the Alzheimer's disease risk factor APOE. *Cancers* (*Basel*), 12: 3842.

https://doi.org/10.3390/cancers12123842