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Mini-Review: Cognitive Complications of Cancer and Cancer-Related Treatments – Novel Paradigms

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Abstract

As advances in diagnostics and therapeutic strategies in oncology have increased the number of cancer survivors, the investigation of the mechanisms associated with long-term cognitive complications of cancer treatment has become an important topic of interest. The neurotoxic effects of chemotherapeutic agents have been described in pre-clinical and clinical research. *In vitro* and rodent studies have identified some underlying mechanisms contributing to chemotherapy-induced neurotoxicity and cognitive impairment for various chemotherapy drugs and other cancer treatments. However, investigation of the direct biological effects of cancer and other potential contributing factors in the pathogenesis of cancer-related cognitive impairment (CRCI) has only recently come into focus. This review will highlight evidence from pre-clinical tumor-bearing rodent models suggesting that cancer influences the cognitive and behavioral changes reported in human cancer populations through direct or indirect pathways that alter the normal neuroinflammatory responses, induce structural brain deficits, and decrease neurogenesis. We reflect on human clinical cancer research indicating that cognitive and behavioral changes precede cancer treatment in some malignancies. We also highlight implications for future areas of CRCI research based on novel findings on the interplay between cancer, chemotherapy, inflammation, tau pathology, and dysregulation of the microbiota-gut-brain axis.

Keywords: cancer-related cognitive impairment; cancer; chemotherapy; microbiota-gut-brain axis; neuroinflammation

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1. Introduction

Cancer-related cognitive impairment (CRCI, also referred to as 'chemo-fog' or 'chemo-brain'), is defined as the neurocognitive deficits experienced by cancer survivors, that may be provoked by cancer and cancer treatments. CRCI is associated with impairments in learning and memory, attention, executive function, and processing speed. Executive function is the control system that manages other cognitive processes; it is regulated by the prefrontal cortex and allows one to mentally organize and regulate information to modulate a response based on environmental cues. Impairments in executive function may result in difficulties in planning, organizing, verbal fluency, processing, storing, and or retrieving information[1]. These impairments diminish cancer survivors' quality of life (QoL)[2].

The earliest clinical reports concerning the emotional and cognitive status of cancer patients date back to the 1970s[3-7]. Initially, reports attributed the behavioral changes experienced by cancer patients to emotional distress and anxiety associated with the cancer diagnosis[8]. Reports on psychiatric referrals of hospitalized cancer patients found that patients' cognitive difficulties were often misdiagnosed as depression and were underreported by clinicians and patients[3, 9]. Weiss et al. provided one of the first detailed reports on the clinical manifestations, incidence, and neurological complications associated with commonly used antineoplastic drugs for the treatment of non-central nervous system (CNS) malignancies, suggesting that the incidence of neurological complications in cancer patients would continue to rise as advances in cancer treatment increased patient survival[10, 11]. Silberfarb et al. found that cancer patients receiving chemotherapy demonstrated lower cognitive functioning compared to non-chemotherapy cancer patients, independently of depression or anxiety[12]. However, it was not until the 2000s that neuroimaging and cognitive studies of breast cancer patients convincingly demonstrated that the cognitive detriments experienced by cancer patients had a biological basis[13, 14]. Research on the neural, molecular, and cellular mechanisms associated with CRCI and cancer contributions to cognitive impairments has also come into focus much more recently[15-19].

This review highlights CRCI in non-CNS cancers in clinical and pre-clinical studies, focusing on the biological contribution of cancer to impaired cognitive function and behavioral changes. We will also describe potential mechanisms and evidence from multidisciplinary studies supporting the need for insight from interdisciplinary fields to further CRCI research (**Fig. 1**).

2. Clinical neuroimaging and cognitive studies

The majority of clinical studies on CRCI have focused on breast cancer survivors, as this population regularly reports experiencing cognitive impairments during and after treatment. Acute declines in cognitive function during chemotherapy have been reported in 17% - 75% of chemotherapy-treated breast cancer patients, with 35% of survivors experiencing cognitive impairments years after chemotherapy completion[20]. In one report, a subset of patients (29%) experienced delayed cognitive decline, which was not present at the time of neurocognitive testing during chemotherapy treatment[21]. In this same study, 21% of patients demonstrated impairments at baseline cognitive testing, before systemic chemotherapy administration or other

cancer treatments, compared to age-matched controls. These findings highlight the need to conduct pre-treatment baseline evaluations in clinical studies of CRCI and suggest that additional factors may influence cognitive decline, such as cancer and diminished cognitive reserve, which may predispose a subset of cancer patients to CRCI and dementia with increasing age[21, 22]. Cognitive reserve is defined as the overall cognitive capacity and is influenced by genetic and epigenetic factors, education, training, and environmental factors[23].

Clinical studies have revealed that declines in neurocognitive function correlate with structural brain changes, including lower gray and white matter density in frontal and temporal brain regions and hippocampal atrophy. Magnetic resonance diffusion tensor imaging (DTI), a technique used to map white matter connectivity via the diffusion of water molecules, has been used to examine white matter integrity in chemotherapy-treated patients. A longitudinal study of young premenopausal (43 years at baseline) breast cancer patients found microstructural white matter changes, which significantly correlated with decreased performance on attention and verbal memory tests 3-4 months after chemotherapy completion compared to the baseline assessment[24]. A follow-up study in the same cohort of patients 3-4 years after chemotherapy completion revealed a recovery to baseline performance in neurocognitive tasks and structural white matter alterations[25]. Other longitudinal studies in breast cancer survivors have reported a time-dependent recovery in cognitive performance 1-4 years after chemotherapy completion[26, 27]. In contrast, a separate study examining the long-term effects of adjuvant chemotherapy on neurocognitive function in breast cancer survivors (n=196) 20 years after treatment found that they performed worse on tasks assessing verbal memory, processing speed, and psychomotor speed, compared to a large population-based group without a history of cancer (n=1,509)[28]. Together these findings point to the discrepancies between different methodologies used in CRCI studies and suggest that a subset of cancer survivors are vulnerable to long-term neurological sequelae that may detrimentally affect their quality of life *years* after completing chemotherapy treatment.

Several studies have also examined hippocampal volume alterations and their association with cognitive function. Apple et al. performed a cross-sectional study that examined hippocampal volume in 16 breast cancer survivors 18 months after adjuvant chemotherapy (doxorubicin, paclitaxel) and estrogen-blockade therapy (tamoxifen) compared to 18 healthy controls[29]. Cancer survivors had significantly smaller hippocampal volumes than controls, increased self-reported cognitive difficulties, and episodic memory impairments. Given the study's cross-sectional design, it is unclear whether the breast cancer survivors experienced cognitive decline or hippocampal atrophy following chemotherapy completion relative to before treatment. It is also unclear whether chemotherapy, tamoxifen, or a combination of both, contributed to changes in hippocampal volume as tamoxifen has been shown to impair working memory and induce structural changes in the prefrontal cortex and hippocampus independently of chemotherapy[30, 31]. Bergouignan et al. also observed hippocampal atrophy (8% volume reduction) and impairments in episodic memory in breast cancer survivors, 18-36 months after treatment completion (surgery, chemotherapy, radiation) relative to controls[32]. Functional neuroimaging studies of breast cancer survivors revealed altered hippocampal connectivity 5-6 months after chemotherapy treatment using resting-state functional magnetic resonance imaging (Rs-fMRI), which correlated with executive function, planning, and working memory impairments[33, 34].

The clinical evidence shows that there is a neurobiological basis underlying the cognitive impairments associated with CRCI. In particular, these neurocognitive impairments are consistent with dysfunction in the hippocampus and frontal cortex brain regions[35]. Multiple

factors may influence the development of CRCI, including age, class of chemotherapeutic agents, and other therapeutic strategies (radiation, hormone-blockade therapies, surgery). However, there are discrepancies in the literature regarding clinical neuropsychological assessments, which should be addressed using validated neuroscientific approaches to investigate CRCI[23]. Subjective reports of cognitive impairments do not necessarily correlate with objective neuropsychological testing results, Horowitz et al. attribute this to the diffuse brain damage associated with CRCI, which may be under-detected, given that these tests were initially designed to detect focal lesions[23]. The effects of cognitive reserve, cancer, epigenetic, and genetic factors on cognition may be masked in cross-sectional comparisons (e.g., to cancer patients not treated with chemotherapy or healthy controls) compared to longitudinal assessments where comparisons are made to a patient's pre-treatment baseline. The lack of a standardized battery of cognitive tests to examine CRCI also contributes to the broad estimate (17% - 75%) of CRCI prevalence in the literature.

3. Tumor-bearing rodent models in pre-clinical studies

Multiple interweaved factors have been proposed to underlie cancer patients' cognitive and behavioral changes, including age, tumor biology, genetic risk factors, cancer treatments, and emotional distress associated with the cancer diagnosis. Studies using tumor-bearing rodent models who are not treated with chemotherapy, yet experience attention, learning, and memory-related behavioral changes suggest that biological factors associated with cancer contribute to cognitive changes in CRCI, independently of chemotherapy and the emotional distress associated with a life-altering diagnosis[36-38].

Tumor-bearing rodent models are needed to examine cancer's potential contributions to cognitive function and its interplay with cancer treatments[39, 40]. Although there have been advances in developing tumor-bearing rodent models of CRCI in the past decade[37, 41-43], examination of delayed behavioral changes in cancer-bearing rodents treated with clinically used chemotherapy regimens is limited[36, 44]. Winocur et al. compared the neurotoxicity of methotrexate (MTX) + 5-fluorouracil (5-FU) and subsequent development of cognitive impairments in the FVB/N-Tg (MMTV-*neu)* 202 Mul/J female transgenic mouse model of breast cancer to non-cancerous wild-type controls[36]. Tumor-bearing mice and wild-type controls treated with MTX + 5-FU had impairments in hippocampal- and frontal-cortex dependent cognitive tasks. Notably, tumor-bearing mice not treated with chemotherapy also had impaired performance in these tasks. Non-treated tumor-bearing mice exhibited increased production of circulating pro-inflammatory cytokines, i.e., interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and monocyte chemoattractant protein-1 (MCP-1)[45]. To examine if the factors secreted by tumor cells induce cognitive impairment, Walker et al. injected 4T1.2. tumor cell-conditioned medium into BALB/c mice daily for nine days[46]. 4T1.2. is an epithelial breast cancer cell line syngeneic to BALB/c mice. Mice injected intraperitoneally with tumor cell-conditioned media did not have significantly different body mass or locomotion changes; however, on day nine of tumor conditioned media injection, they showed deficits in hippocampal- and frontal cortex-dependent learning, compared to mice injected with the non-tumor conditioned medium. On day nine of conditioned-media injection, mice that received tumor-cell conditioned media showed deficits in hippocampal- and frontal cortex-dependent learning memory[46]. Additional investigation is necessary to determine the duration of these impairments after discontinuing systemic exposure to tumor-conditioned medium in this model. Comparison of plasma cytokine levels in mice with tumors and mice that were injected with tumor cell-conditioned medium revealed a similar inflammatory profile, with elevated levels of interleukin-1 alpha (IL-1α), IL-6, granulocyte colony-

stimulating factor (G-CSF), and the chemoattractant macrophage inflammatory protein-1 alpha (MIP-1α). In a separate study, Yang et al. showed that female BALB/c mice bearing colon carcinoma cell peripheral tumors (colon carcinoma cell line, CT26) demonstrated a 1.68-fold increase in plasma corticosterone levels and significantly higher adrenal gland weights compared to the non-tumor controls, 14 days post-tumor inoculation[37]. These changes were accompanied by elevated mRNA expression of IL-6 and TNF-α pro-inflammatory cytokines in the hippocampus and high IL-6 levels in plasma.

Although further studies are needed to examine the combined effect of cancer and cancer treatment on cognitive function long-term, there is strong evidence implicating inflammatory mechanisms in CRCI, which will be discussed in the following section.

4. Neuroinflammation

Inflammation is one of the hallmarks of cancer, and the connection between inflammation and changes in learning and memory have been described in aging and neurological disorders independently of cancer and its treatment[47-51]. Increased circulating levels of pro-inflammatory cytokines have been found to correlate with cognition changes in breast[52, 53], and testicular cancers[54]. Chemotherapeutic agents, many of which cannot cross the BBB or do so at low concentrations, can indirectly induce neuroinflammation via an increase in pro-inflammatory cytokines in the periphery. Although the BBB remains poorly understudied in the context of cancer and CRCI, it is plausible that systemic inflammation induced by specific chemotherapy agents and cancer may disrupt or alter the integrity of the BBB[55]. Tumor-induced production of pro-inflammatory cytokines as well as those elicited by chemotherapy may contribute to behavioral changes that affect cognitive function in cancer patients[40, 56, 57], since many of the upregulated cytokines during cancer progression can cross the BBB, including TNF-α[58], IL-6[59], and interleukin-1 beta (IL-1β)[60].

As the resident macrophages in the CNS, microglia play an essential role in neuroimmune surveillance and CNS homeostasis maintenance. Microglia are involved in various processes including synaptic pruning, programmed cell death, neurogenesis, myelin turnover, and phagocytic debris removal, functions which are critical for the maturation and plasticity of neural circuits[61]. Release of pro-inflammatory cytokines and immune mediators under systemic inflammation can activate microglia and increase the local production of pro-inflammatory cytokines in the brain[62]. Under transient systemic inflammation, microglia migrate to the cerebral vasculature to maintain BBB integrity; however, prolonged inflammation phenotypically alters microglia, resulting in the phagocytosis of astrocytic end-feet and compromises BBB integrity, resulting in widespread neuroinflammation and a leaky BBB[63]. Activated microglia and astrocytes are observed in many mouse models of Alzheimer's disease (AD)[64], traumatic brain injury (TBI)[65], ischemia, and stroke[66].

Microglia depletion can mitigate neuroinflammation in rodent models of CRCI. Gibson et al. showed that microglia depletion using the colony-stimulating factor 1 receptor (CSF1R) inhibitor, PLX5622, reduced astrocyte reactivity, normalized myelination, and prevented MTX-induced cognitive deficits in a juvenile mouse model[67]. PLX5622 has also been shown to ameliorate cognitive deficits in rodent models of AD[68], cranial radiation[69], and TBI[70]. Microglial activation and increased pro-inflammatory cytokine/chemokine gene expression in the brain has also been observed following paclitaxel chemotherapy[71]. Loman et al. examined the changes in peripheral immune system activation, cognition, and microglia immune reactivity in mice treated with paclitaxel[71]. Paclitaxel-treated mice had elevated levels of IL-1β, TNF-α, IL-6, and the chemoattractant Cxcl1 in the plasma, which was associated with increased expression of IL-1β,

TNF-α, IL-6, Cxcl1 mRNA transcription in the brain, and correlated with fatigue and cognitive impairments, but no evidence of microglial activation. Interestingly in rodent models of paclitaxel-induced peripheral neuropathy, astrocytic activation but not microglial activation has been observed in the spinal dorsal horn[72], suggesting that although paclitaxel may induce neuroinflammation, microglial activation may not be involved or may only be transiently activated shortly following paclitaxel exposure. Microglial inflammation plays a central role in the pathobiology of neurological sequelae of many commonly used cancer therapies, including radiation[69], MTX[73], and cyclophosphamide[74], doxorubicin[75], but prolonged microglial activation and neuroinflammation have not been observed following exposure to cisplatin[76] and 5-FU[77] in rodent models.

CNS inflammation is associated with breakdown of the BBB and recruitment of peripheral immune cells in multiple neurodegenerative disorders[78, 79]. Astrocytes are integral to the formation and maintenance of the BBB, and bidirectional crosstalk between astrocytes and microglia modulate CNS inflammation through the secretion of cytokines and inflammatory mediators and recruitment of peripheral immune cells into the CNS[78, 80]. Astrocytes promote the activation of microglia through the secretion of IL-6, granulocyte-macrophage colony–stimulating factor (GM-CSF), TNF-α, and other signaling factors [78, 81, 82]. The secretion of IL-1α , TNF-α, and complement component 1q (C1q) has been shown to induce a neurotoxic phenotype in reactive astrocytes in models of lipopolysaccharide (LPS)-induced neuroinflammation[83]. Based on the role of astrocytes in mediating neuroinflammation and maintaining BBB integrity, astrocyte involvement in CRCI is plausible yet pre-clinical evidence in chemotherapy-treated rodents and non-CNS tumor-bearing rodents is limited. Demers et al. found that systemic inflammation including elevated levels of plasma IL-6 and blood neutrophils in a subcutaneous model of Lewis lung carcinoma in C57BL/6 mice was associated with an increase in astrocyte activation and fibrin accumulation in the blood vessels of the brains of tumor-bearing mice compared to controls, however there was no significant change in BBB integrity at 17 days post-transplantation[84]. Gibson et al. demonstrated that microglia activation induced by MTX exposure in C57BL/6 mice, increased astrocyte reactivity which was associated with neuronal and oligodendrocyte cell death, and impaired oligodendroglial differentiation[85].

Among other functions, astrocytes provide vital support for neurons in health and during development, they secrete neurotrophic factors, i.e., brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), to regulate synaptogenesis, neuronal differentiation, and neuronal survival[86]. In a recent study, English et al. examined the neuroprotective effects of astrocytes in mitigating cisplatin-induced neurotoxicity. Exposure of primary cortical neurons to cisplatin depolarized neuronal mitochondrial membrane potential, altered neuronal calcium dynamics, and reduced neuronal survival. The co-culture of cisplatin-treated neurons with astrocytes restored neuronal calcium dynamics, mitochondrial membrane potential, and increased neuronal survival via astrocytic mitochondrial transfer via the mitochondrial Rho GTPase-1 protein (Miro-1)-dependent pathway[87]. Notably this and other studies have shown that neurons are more sensitive to cisplatin than astrocytes, which suggests that astrocytic mitochondrial transfer might mitigate neuronal mitochondrial damage and neurotoxicity in the brain after acute cisplatin exposure[15, 87]. However, extensive neuronal damage under chronic cisplatin exposure and potential reactive astrogliosis may contribute to the development of CRCI, although further investigation in rodent models is clearly warranted.

Additional studies in tumor-bearing rodents are needed to elucidate the individual and combined effects of cancer and chemotherapy on neuroinflammatory processes and subsequent effects on learning and memory.

5. Neuronal/Oligodendroglial Damage

Neurogenesis is central to the integrity and plasticity of the hippocampus; reduced neurogenesis in aging and neurodegenerative disorders has been linked to cognitive impairments and mood disorders (anxiety, depression)[88, 89]. Impaired hippocampal neurogenesis following chemotherapy treatment may contribute to cognitive changes associated with CRCI[90]. Neural stem/progenitor cells (NSC) are crucial to intact memory, and hippocampal function throughout life; toxicity to NSC and decreased neurogenesis may contribute to the neurocognitive impairments experienced by cancer survivors[16]. In humans, postmortem analysis of hippocampal tissue from medulloblastoma or leukemia patients within 2-23 years following chemotherapy completion revealed a profound reduction in neurogenesis. The number of immature neurons (DCX+) was decreased 10 to 100-fold in patients receiving chemotherapy plus radiation relative to age- and sex-matched control subjects[91].

Rodent studies have elucidated the effects of chemotherapy on hippocampal NSC and neurons. Our studies and others have shown both *in vitro* and *in vivo* that neural progenitor cells and post-mitotic neural cells, including neurons and oligodendrocytes, are preferentially susceptible to damage by diverse types of chemotherapeutic agents, as compared to human cancer cell lines[15, 92-94]. At clinically relevant concentrations that kill 40-80% of cancer cells, the DNA targeting agent, cisplatin, has been shown to reduce the viability of human and rat primary CNS progenitor cells by 70-100%[15]. Sub-lethal doses of cisplatin and other DNA-targeting agents reduce the self-renewal capacity of neural progenitor cells, decrease the number of SOX2+ progenitor cells in the dentate gyrus, and induce dendritic branching and spine density loss in hippocampal neurons[15, 92, 94].

Chronic treatment with clinically equivalent doses of cyclophosphamide or doxorubicin impaired performance on hippocampus-dependent tasks in treated rats compared to untreated controls. Assessment of hippocampal neurogenesis at three weeks post-treatment revealed a 47% - 53% decrease in DCX+ neurons and an 81%-88% drop in BrdU-NeuN+ cells compared to the saline-treated controls[95]. The DCX+ neurons displayed abnormal dendritic morphology and ectopic migration. These results suggest that a decline in hippocampal neurogenesis is associated with disrupted hippocampal-based cognitive function in CRCI and that neuroprotective strategies to preserve hippocampal neurogenesis may be useful in ameliorating CRCI[95]. In a follow-up study, human NSC transplantation in the rat model of chronic cyclophosphamide-treatment reduced cognitive impairments[74]. The grafted NSC survived (8%) and differentiated along neuronal and astroglial lineages, and importantly enhanced neuronal dendritic arborization and spine density. As only 8% of transplanted NSC survived, a plausible mechanism for reversing the deleterious effects of CRCI with stem cells may be through trophic support via secretion of neurotrophic factors (e.g., BDNF, NGF) that preserve neuronal integrity and synaptic plasticity.

Clinical neuroimaging studies have revealed a loss of white matter structural integrity in breast cancer survivors[96, 97]. Chemotherapy-induced white matter damage, including loss of oligodendrocytes, and demyelination has been widely described for MTX and 5-FU[77, 85]. Gibson et al. showed that frontal lobe postmortem tissue samples of individuals treated with chemotherapy contain fewer oligodendrocytes and oligodendrocyte precursor cells (OPC) than samples from control subjects. Also, MTX treatment in mice decreased myelin sheath thickness in the white matter and a long-term decrease in proliferating and mature OPC compared to control mice, suggesting that OPC survival and maturation are impaired[85]. Notably, stimulating BDNF-TrkB

signaling, using the small molecule LM22A-4, rescued MTX-induced myelin loss and cognitive impairment[98].

Using a cellular approach, Chiu et al. demonstrated that nasal mesenchymal stem cells (MSC), administered after cisplatin discontinuation, migrated into the brain, restored white matter integrity, and reversed cisplatin-induced cognitive impairments, including deficits in working memory, spatial recognition, and executive functioning[99]. Cisplatin altered the brain expression profiles of genes involved in oxidative phosphorylation and mitochondrial function. Also, MSC administration restored mitochondrial respiratory function and morphology following cisplatin treatment in brain synaptosomes. Further studies revealed that MSC nasal administration prevented the cisplatin-induced loss of hippocampal neural progenitor cells in mice. Mitochondrial transfer to NSC restores cisplatin-induced mitochondrial integrity changes by normalizing membrane potential and respiratory function and promoting NSC survival[100]. Although further investigation on how MSC-derived mitochondria communicate with the damaged acceptor NSC cellular machinery to improve NSC survival and rescue mitochondrial function is needed, these studies, along with others, crucially demonstrate the role of impaired neurogenesis and neuronal damage in CRCI.

6. Tau pathology

The microtubule-associated protein tau, which is abundantly expressed in neurons of the CNS, plays an essential role in the assembly and stability of axonal microtubules and regulates neurite outgrowth[101]. Tau hyperphosphorylation and aggregation in neurofilament tangles reduce microtubule stability and decrease axonal transport[102]. Tau dysregulation is involved in the pathogenesis of various neurodegenerative diseases, notably in AD, TBI, and Parkinson's disease (PD) [103]. Elevated cerebrospinal fluid (CSF) levels of tau have been used as a biomarker of AD, and correlate with impaired cognitive function in neurocognitive testing[104].

Although tau has been typically studied in neurodegenerative diseases, it is not exclusive to neurodegeneration, rather elevated tau levels are recognized as a biomarker of brain injury. Recent studies in acute lymphoblastic leukemia (ALL) and breast cancer survivors have examined the association between tau and cognition[105-107]. Protas et al. assessed tau levels in CSF samples from children with ALL treated with intrathecal MTX and assessed cognitive function 3.7 years after diagnosis. Elevated tau levels in the CSF after consolidation chemotherapy were associated with decreased verbal memory 3.7 years after diagnosis[106]. A follow-up study found that the high CSF tau levels measured at treatment completion correlated with poor performance in neurocognitive tasks six years after treatment completion, suggesting delayed chronic cognitive complications in ALL survivors[105]. Henneghan et al. explored the association between serum levels of tau, amyloid-β, and pro-inflammatory cytokines in chemotherapy-treated breast cancer survivors[107]. Findings suggest an interplay between tau and inflammatory responses to influence cognitive functioning, although further studies are needed to determine whether serum tau levels correlate with cognitive impairments in breast cancer survivors.

Tau pathology has also been linked to cisplatin-induced cognitive impairments in pre-clinical studies. Cisplatin treatment in C57BL/6 mice induced a significant increase in α-tubulin deacetylation and accumulation of hyperphosphorylated tau in the brain, which indicates disruption of microtubule stability[108]. Cisplatin administration in adult (7-8 month-old) C57BL/6 mice resulted in delayed cognitive impairments and an increased tau expression in the hippocampus 4 months after cisplatin discontinuation. The increase in hippocampal tau clusters was associated with a decreased synaptic integrity in cisplatin-treated mice compared to age-matched 11-12 month-old control mice[109]. Mouse models of MTX-induced CRCI have also

provided evidence of tau dysregulation. MTX treatment in 2 week-old C57BL/6 pups resulted in transient increases in CSF tau and reduced hippocampal cell proliferation, which resulted in hippocampus-dependent cognitive impairments in adulthood, 3-4 months after MTX completion[110]. These findings suggest that tau dysregulation is indicative of neuronal damage and synaptic dysfunction associated with chemotherapy treatment. Additional studies are needed to determine whether the acute changes in tau levels observed in cancer patients and pre-clinical models result in long-lasting aberrant tau (accumulation or hyperphosphorylation) in the brain and whether serum tau levels can serve as a potential biomarker of CRCI.

7. Microbiota-gut-brain axis dysregulation

The microbiota-gut-brain axis refers to the bidirectional communication system between gut microbes, the enteric nervous system (ENS), and the CNS via neural, endocrine, immune, and humoral pathways[111, 112]. Chemotherapy has been shown to adversely affect the gut microbiota composition in pediatric and adult cancer populations. Gastrointestinal (GI) issues are frequent and dose-limiting toxicities of chemotherapy treatment that may reduce cancer treatment adherence and affect survival. Chemotherapy-induced GI toxicities are due to disruption of the gut microbiota, termed dysbiosis, inflammation (intestinal and systemic), and mucositis, which is the ulceration of the oral/GI tract mucosal cell lining. Mucositis affects over 80% of cancer patients treated with high-dose chemotherapy[113, 114]. Huang et al. examined changes in the intestinal microbiota composition of 36 pediatric ALL patients treated with high-dose MTX, compared to 36 healthy age-matched controls[115]. Intestinal microbes decreased in the stool samples of the ALL group post-chemotherapy completion by 29.6% compared to the controls. MTX-induced changes in the gut microbiota composition were evident one-week post-treatment completion and at least 9 months after cessation of chemotherapy in a separate study of ALL survivors[116]. Additional studies suggest that chemotherapy treatment results in reduced gut microbiota diversity, leading to mucositis, inflammation, and long-term microbiota dysbiosis[117, 118].

The intestinal microbiota's ability to influence CNS function, cognition, and behavior has sparked interest recently. Alterations in gut microbiota have been implicated in the pathogenesis of various neurological disorders involving changes in cognition and emotional behavior which include, AD[119], autism spectrum disorders (ASDs)[120], Major Depressive Disorder (MDD)[121, 122], PD[123], and schizophrenia[124]. These disorders are also associated with neuroinflammation. There are multiple pathways proposed by which intestinal mucositis and decreased GI microbiota diversity provoked by chemotherapy treatment may contribute to CRCI, including endocrine and neural signaling pathways via the enteric nervous system[125] and systemic inflammation[118, 126]. Pre-clinical studies of rodent models treated with platinum-based chemotherapy (cisplatin, carboplatin, oxaliplatin) have described oxidative stress and mitochondrial dysfunction as the underlying mechanisms of cognitive impairments[94, 127, 128], peripheral neuropathy[129-131], and neural cell damage elicited by these agents[15, 92]. However, the influence of chemotherapy on the ENS function and the extent to which GI dysfunction influences cognition and behavior needs further exploration. The ENS is a large component of the autonomic nervous system and is responsible for the GI tract's physiological functions, including motility, secretion of gastrointestinal enzymes, and blood flow[132]. Located within the GI tract wall, the ENS contains 200-600 million neurons, which are distributed into two types of ganglia, myenteric and submucosal plexuses[133]. Using a mouse model, Wafai et al. demonstrated that chronic oxaliplatin administration in BALB/c mice increased the expression of neuron nitric oxide synthase (nNOS), decreased myenteric neurons of the distal colon, and reduced colonic motility[134]. Chronic cisplatin administration reduced GI

and colonic motor function, reduced the number of colonic myenteric neurons, and increased nNOS+ myenteric neurons[135]. Similar findings have been reported for 5-FU, which is the first-line chemotherapy for colorectal cancer. McQuade et al. found that increased GI transit and acute intestinal inflammation (increased levels of fecal lipocalin-2 and CD45+ leukocytes in the colon) preceded myenteric neuronal loss and reduced colonic motility in BALB/c mice treated with a clinically relevant regimen of 5-FU[136].

Using a clinically-relevant regimen of paclitaxel chemotherapy in adult female BALB/c mice, Loman et al. found that paclitaxel transiently increased expression of pro-inflammatory cytokine (IL-1β, IL-6, and TNF-α) and chemokine (CXCL1) mRNA levels in the brain (hypothalamus, hippocampus), circulating levels of LPS binding protein (LBP), IL-1β, TNF-α, and CXCL1[71], and impaired context discrimination. Paclitaxel-treated mice had altered microbiota composition and increased colon crypt depth. Reductions in fecal and colonic microbiome diversity and loss of colonic tissue integrity have been shown in other studies to contribute to anxiety and depression[137, 138]. In a recent study, Zhang et al. found that 5-FU treatment in rats significantly increased immobility time in the tail suspension test and decreased sucrose consumption in the sucrose preference test, two common rodent behavioral tasks used to assess rodent depression-like behavior[139]. In addition to these behavioral changes and reduced gut microbiome diversity, 5-FU increased gamma-aminobutyric acid (GABA) levels, the most abundant inhibitory neurotransmitter in the CNS. Fecal microbiota transplants from healthy controls into 5-FU treated rats reversed depressive-like behaviors.

The microbiota-gut-brain axis plays a significant role in the development of various neurological disorders. Current studies have demonstrated that chemotherapy may induce ENS toxicities and gut microbiota changes, may influence neurocognitive function. Further studies are warranted to elucidate the effects of cancer and cancer treatment (chemotherapy, radiation, immunotherapy) on gut microbial composition in cancer patients and pre-clinical rodent models. Understanding the mechanisms by which chemotherapy alters ENS and GI microbiome diversity is also of interest for developing new treatment strategies that can diminish CRCI and GI toxicities.

8. Summary and conclusions

As the number of cancer survivors continues to rise, an improved understanding of the biological mechanisms associated with CRCI becomes more crucial for developing potential therapeutic strategies to minimize the cognitive and neurotoxic adverse sequelae of cancer and cancer treatments in survivors. In this review, we have highlighted clinical and pre-clinical evidence of non-CNS tumors affecting cognition and the potential mechanisms by which tumors may, directly and indirectly, influence cognitive function. We have also highlighted recent findings implicating cancer-induced inflammation, tau pathology, neuronal/oligodendroglial damage, and microbiota-gut-brain axis dysfunction in the pathogenesis of CRCI.

Several challenges remain in the clinical and pre-clinical CRCI research settings. Currently, standardized neurocognitive assessments of CRCI in patients are lacking, and subjective complaints of CRCI do not correlate with the results of neurocognitive evaluations, which is reflected in the reported range (17% – 75%) of cancer survivors who experience CRCI[23]. Although clinical neuropsychological tests have found significant effects of cancer treatment on cognition, these measures do not account for the subtle cognitive difficulties associated with CRCI as they were developed to diagnose severe brain pathologies, such as AD, PD, and TBI. Recent neuroimaging longitudinal studies in breast cancer survivors have revealed that structural changes in white matter integrity correlate with altered cognitive function[24, 25]. Such studies have

demonstrated the essential yet challenging need of examining baseline cognitive performance and structural MRI analysis in cancer patients before initiating treatment, in addition to assessment at multiple time-points during and after treatment completion. In pre-clinical studies, the use of tumor-bearing rodent models treated with clinically used cancer regimens is needed to characterize further the mechanisms associated with CRCI and test therapeutic interventions. Interdisciplinary approaches spanning diverse methodologies, including microbiology, gut biology, basic neuroscience, aging biology, and tumor biology, will be essential to leverage the field of CRCI and help develop therapeutic interventions to improve the quality of life of cancer survivors.

CRediT authorship contribution statement

Naomi Lomeli: Writing – original draft, Visualization. **Javier Lepe:** Writing – original draft. **Kalpna Gupta:** Writing – review & editing, Supervision, Funding acquisition. **Daniela A. Bota:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition.
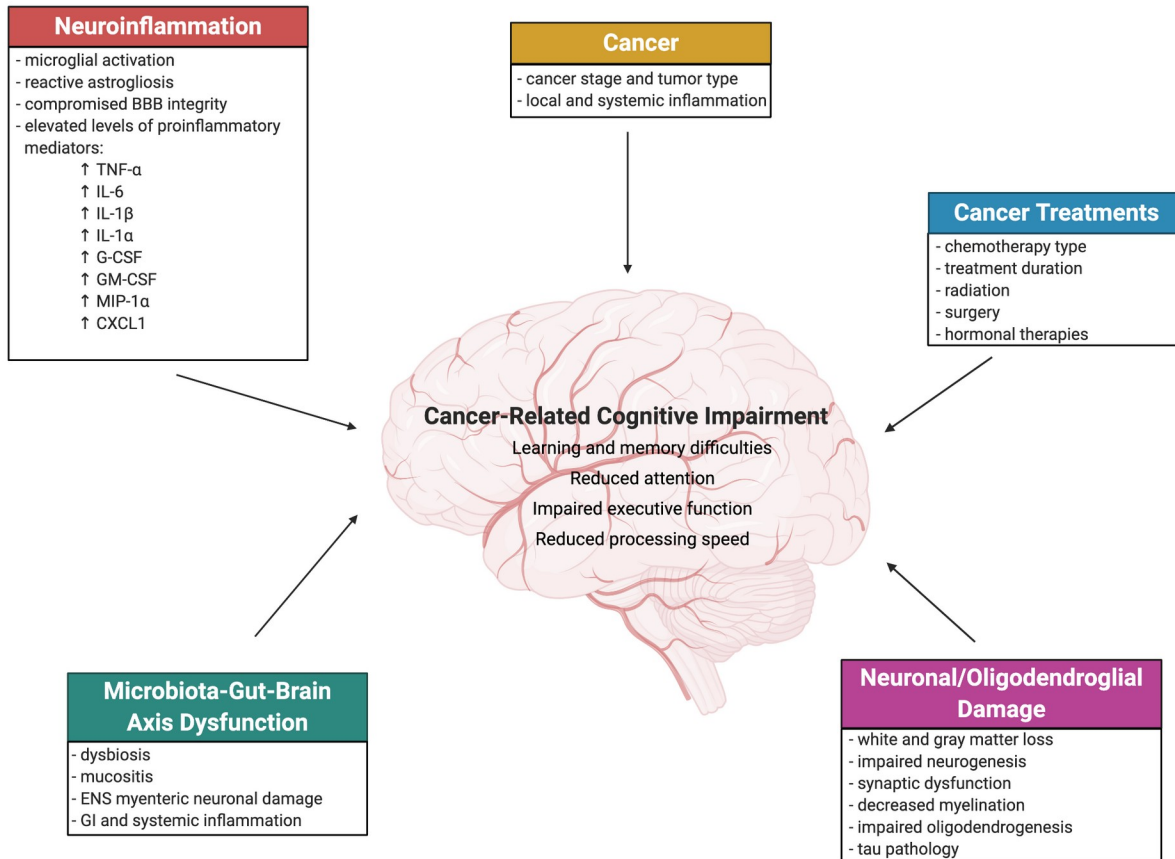
Figure 1. Mechanisms of cancer-related cognitive impairment (CRCI). A simplified schematic providing an overview of mechanisms of CRCI discussed in this review. Cancer-induced cognitive changes may be associated with local and systemic inflammation, and elevated production of proinflammatory mediators, which can induce neuroinflammation. Cancer treatments, in particular chemotherapy which is discussed here, is associated with neuronal/oligodendroglial damage, neuroinflammation, and microbiota-gut-brain axis dysfunction, which can directly or indirectly induce cognitive decline. Cancer and cancer treatments may exert additive detrimental effects on cognition.

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140. Figure 1 was created using BioRender.com