BBA - Molecular Basis of Disease 1865 (2019) 1088–1097

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Review

Plausible biochemical mechanisms of chemotherapy-induced cognitive impairment ("chemobrain"), a condition that significantly impairs the quality of life of many cancer survivors

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ARTICLE INFO

Keywords:
Oxidative damage
Chemotherapy-induced cognitive impairment
TNF-alpha
Blood-brain barrier
Mitochondrial dysfunction

ABSTRACT

Increasing numbers of cancer patients survive and live longer than five years after therapy, but very often side effects of cancer treatment arise at same time. One of the side effects, chemotherapy-induced cognitive impairment (CICI), also called "chemobrain" or "chemofog" by patients, brings enormous challenges to cancer survivors following successful chemotherapeutic treatment. Decreased abilities of learning, memory, attention, executive function and processing speed in cancer survivors with CICI, are some of the challenges that greatly impair survivors' quality of life. The molecular mechanisms of CICI involve very complicated processes, which have been the subject of investigation over the past decades. Many mechanistic candidates have been studied including disruption of the blood-brain barrier (BBB), DNA damage, telomere shortening, oxidative stress and associated inflammatory response, gene polymorphism of neural repair, altered neurotransmission, and hormone changes. Oxidative stress is considered as a vital mechanism, since over 50% of FDA-approved anti-cancer drugs can generate reactive oxygen species (ROS) or reactive nitrogen species (RNS), which lead to neuronal death. In this review paper, we discuss these important candidate mechanisms, in particular oxidative stress and the cytokine, TNF-alpha and their potential roles in CICI.

1. Introduction

With advances in science and technology for treatment of cancer, the number of cancer survivors continues to increase. There were more than 15.5 million cancer survivors at the end of 2015, and this number could rise to 20 million in the next 10 years [1]. However, a significant consequence of cancer chemotherapy often occurs that affects the quality of life of cancer survivors. Cognitive dysfunction may happen acutely or after a period following chemotherapy. The phenomenon, called chemotherapy-induced cognitive impairments (CICI), "chemobrain" or "chemofog", can be subtle or severe. CICI can retard recovery to normal life for cancer survivors, and this condition involves loss of

Abbreviations: 8-oxoG, 8-oxoguanine; ABCA1, ATP-binding cassette transporter; AD, Alzheimer disease; AP, apurinic/apyrimidinic; APE1/APEX1, apurinic/apyrimidinic endonuclease 1; ApoA1, apolipoprotein A-I; APOE, apolipoprotein E; BBB, blood-brain barrier; BCNU, carmustine; BDNF, brain-derived neurotrophic factor; BER, base excision repair; CICI, chemotherapy-induced cognitive impairment; CNS, central nervous system; COMT, catechol-*O*-methyltransferase; COX-2, cyclooxygenase 2; cyt *c*, cytochrome *c*; Dox, doxorubicin; DTX, docetaxel; FDA, food and drug administration; GCEE, γ-glutamyl cysteine ethyl ester; GIGT, chemotherapy-induced gut toxicity; GSH, glutathione; HNE, 4-hydroxynonenal; IL-1β, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; JAK2, janus kinase 2; MDA, malondialdehyde; MDR1, multidrug resistance protein; MnSOD, mitochondrial antioxidant manganese superoxide dismutase; MRI, magnetic resonance imaging; MRP1, multidrug resistance-associated protein-1; NAC, *N*-acetyl cysteine; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOR, novel object recognition; $O_2^{-}\cdot$, superoxide; OGG1, 8-oxoguanine DNA glycosylase; PC, protein carbonyl; PD, Parkinson's disease; PET, positron emission tomography; P-pg, permeability glycoprotein; PGE2, prostaglandin E_2; RNS, reactive nitrogen species; ROS, reactive oxygen species; SNP, single nucleotide polymorphisms; STAT3, signal transducer and activator of transcription 3; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-alpha

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https://doi.org/10.1016/j.bbadis.2019.02.007
Received 9 November 2018; Received in revised form 5 February 2019; Accepted 7 February 2019
Available online 10 February 2019
0925-4439/

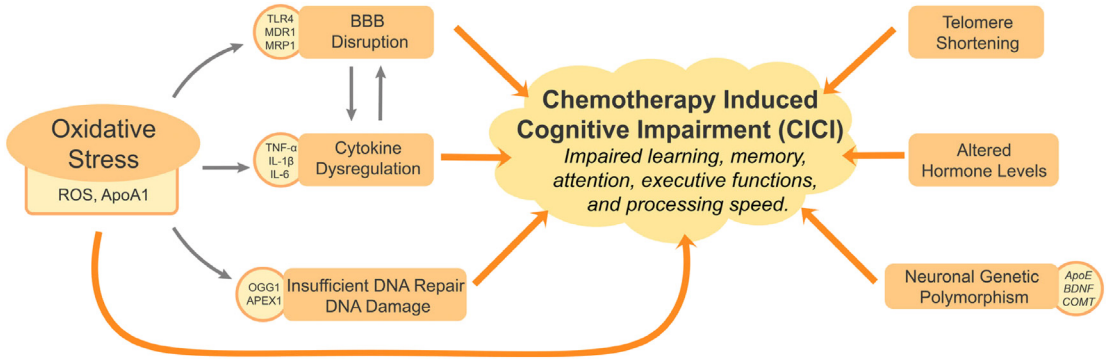

Fig. 1. Summary of candidate interrelated mechanisms of CICI discussed in this review paper.

memory and learning ability, less attention and concentration, decreased executive function, and slower processing speed [2–5].

A cancer with a substantial percentage of survivors is breast cancer [5]. However, 35%–70% of breast cancer survivors reported cognitive impairment after or even during the treatment [6]. Cognitive impairment affects one third of childhood cancer survivors [7]. In a national cross-sectional study, participants who had a cancer history reported memory impairment 40% more than those without cancer [8]. In a recent study, 65% of breast cancer patients experienced acute cognitive impairment and 61% of them had late cognitive decline, compared to 21% of patients had cognitive dysfunction before chemotherapy [9]. CICI can even last 20 years post-chemotherapy for breast cancer [10]. Breast cancer survivors who were treated with cyclophosphamide, methotrexate and fluorouracil about 21 years ago were recruited. Compared to a non-cancer group, the 196 cancer survivors self-reported more memory complains and poorer performance in neuropsychological examinations including verbal memory, processing speed, executive function and psychomotor speed [10]. However, there are also studies showing no significant cognitive changes before and after chemotherapy [11–13].

The central nervous system (CNS) is affected by chemotherapeutic agents, many of which do not cross the blood-brain barrier (BBB) [14]. Chemotherapy could lead to pathological changes such as reduced brain connectivity [15–18]. Consistent with this notion, brain structure and function both are altered in CICI. Volume and density changes of white matter and grey matter of patients who had chemotherapy were determined by MRI [19–22]. Altered prefrontal cortex and hippocampus also are associated with CICI [23–27]. Hippocampus is an area important for learning and memory in brain. Chemotherapy disrupted structure and function of hippocampus and impaired its neurogenesis, leading to cognitive deficits [28].

Functional and structural MRI is a strong tool to demonstrate brains in cancer survivors are different from brains of people not treated with chemotherapeutic agents or healthy people with no cancer, especially in the case patient who did not show big differences on neuropsychological tests compared to her healthy monozygotic twin, but had self-reported cognitive impairment [29]. Such changes indicate that cancer survivors who had chemotherapy have to activate more areas in the brain and make more efforts to maintain the ability of work, even if they show a normal aspect in neuropsychological tests [30]. PET scanning also revealed abnormal glucose metabolism in brain of cancer survivors who had undergone chemotherapy [31,32].

Better understanding of the molecular mechanisms of CICI is important to reduce or even prevent cognitive dysfunction after cancer treatment, with the goal of improving the quality of life of survivors without changing chemotherapeutic efficacy. This is particularly the case for those child patients and adult patients who live longer. However, the mechanisms of CICI still are not fully understood. A complication of CICI is that it is multifactorial in origin, and it shares similar appearances and causes with depression, anxiety and fatigue, which are commonly associated with cancer treatment and cancer *per se* [5,33]. Lack of education and aging could be other confounders [34,35].

Neuronal activity is often altered by chemotherapy [36,37]. Neuronal apoptosis was observed in correlation with cognitive impairments associated with traumatic brain injury, aging, several neurodegenerative disease and chemotherapy [2,38,39]. NMDA receptor antagonists, such as memantine, could reverse the cognitive deficits and protect memory functions by blocking NMDA receptors during chemotherapy treatment [40,41]. Co-administration of the anti-cancer drug, methotrexate, with the NMDA receptor antagonist dextromethorphan reduced the severity of seizures [42]. However, these antagonists can themselves cause significant side effects [43].

As noted above, neuronal death, which underlies CICI symptoms, occurs even though many FDA-approved anti-cancer drugs cannot cross the BBB. Recent studies suggested that decreased integrity of the BBB, low availability of DNA and neural repair processes, decreased antioxidant levels and increased oxidative stress, hormone changes and immune system responses contribute to neurotoxicity, and eventual neuronal death with subsequent cognitive impairments following chemotherapy [2,3,5,44]. The candidate mechanisms are shown in Fig. 1. In this current review paper, we summarize recent important candidate mechanisms of CICI mentioned above, especially cytokines and oxidative stress. We attempt to build a fuller picture of mechanisms of CICI, and thereby for future studies and clinical treatments designed to improve the quality of life of cancer survivors without interference of chemotherapeutic efficacy.

2. Chemotherapy-induced disruption of BBB integrity increases BBB permeability and brain vulnerability

Some commonly used chemotherapeutic agents lead to significantly increased cell death and decreased cell division in multiple areas in brain of mice. CNS progenitor cells and non-dividing oligodendrocytes are more vulnerable to carmustine (BCNU), cisplatin and cytarabine than multiple cancer cell lines [45]. BBB permeability increased after treatment with irinotecan [46]. Dysfunction of the BBB has been recognized in several neurological disorders and many neurodegenerative diseases, including Parkinson's disease (PD) and Alzheimer's disease (AD), both with associated pro-inflammatory states [47–50]. Abnormal BBB integrity leads to direct or indirect neurotoxicity. Furthermore, some chemotherapeutic agents [51], such as BCNU, paclitaxel and 5-fluorouracil, reportedly were detected in low, non-therapeutic concentrations in brains of rodents or primates [52], and these drug levels could potentially contribute to direct harmful effects to the parenchyma. Docetaxel (DTX) led to impaired novel object recognition (NOR) memory of mice in post-treatment behavioral tests, and this drug was detected in brain that demonstrated astrocyte activation [53].

Fully 50% of FDA-approved anti-cancer drugs are ROS-generating agents [2], and ROS can compromise the BBB by triggering several

pathways, including oxidative stress [54]. Increased BBB permeability and disruption allow peripheral toxins and inflammatory mediators able to go into brain easier, especially allow those pro-inflammatory cytokines generated by chemotherapy targeted tissues [52]. Cytokine enters brain by receptor mediated-endocytosis or passive diffusion through the leaky regions of BBB since some pro-inflammatory cytokines disrupt the tight junction of BBB [47,52,55,56], eliciting glia activation and local inflammatory response in brain as a consequence.

Transmembrane protein toll-like receptor 4 (TLR4) is a possible factor influencing on BBB integrity after chemotherapy treatment. Evidence showed TLR4 is involved in chemotherapy-induced gut toxicity (GIGT), and there might be a linkage between GIGT and chemobrain [46,52]. The activation of TLR4 produces pro-inflammatory cytokines and chemokines, as well as leads to activation of intracellular NF-κB [57]. Activation of astrocytes in CNS of WT mice is decreased by the absence of the *TLR4* gene after treatment with irinotecan, indicating a role for TLR4 signaling in chemotherapy-induced neuro-inflammation and neurotoxicity [46].

Multidrug resistance protein (MDR1), also known as permeability glycoprotein (P-pg), and multidrug resistance-associated protein-1 (MRP1) are involved in the neurotoxicity and cognitive impairment after chemotherapy. Elevated expression of MRP1 in heart of doxorubicin (Dox)-treated mice protects heart from induced oxidative stress [58]. Dox also elevated MRP1 activity in mice brain with elevated oxidative stress [59]. Delivery of anti-depression drugs could be improved by decreasing the efflux function and expression of MDR1 [60]. Meanwhile, expression of these proteins could be associated with polymorphism of multidrug resistance genes, implying the level of drugs pumped out of cells and brains could be different in various genotypes [61,62]. However, association between *MDR1* polymorphism and clinical response was not found in chemotherapy-treated Hodgkin's lymphoma patients [63]. Knockout of multidrug resistant genes makes mice more sensitive to the anti-cancer drug vincristine [64]. Therefore, expression of these multidrug proteins at the BBB controls the level of chemotherapeutic drugs in brain and contributes to the prevention of their deleterious impacts on CNS. Drugs or other toxins could cross BBB with a harmful level and lead to cognitive impairment as a consequence if the polymorphism of the *MRP-1* genes decrease the protein function or those proteins are damaged by oxidative stress from the periphery.

3. DNA damage and associated deficits of DNA repair are linked with CICI

DNA damage and deficits of DNA repair systems also are known to be linked with cognitive deficits. Radiotherapy and some classes of chemotherapeutic drugs, such as alkylating or antibiotic agents, operate primarily by damaging the DNA of cancer cells, inducing apoptotic processes [65,66]. Oxidative stress is a main cause of DNA damage in brain cells [67]. Chemotherapy often is associated with ROS/RNS production and oxidative stress, which cause further DNA damage in tissues [14,68]. Moreover, the complex process of normal DNA replication is frequently subject to mistakes and mutations, and such damage requires an efficient repair process that can repair the damaged DNA or lead to cell death *via* apoptosis. The failure of the regular DNA repair process can lead to irreparable modifications, such as double-strands breaks, mismatches and DNA crosslinks that can result in cell death or oncogene activation or inactivation of tumor suppressor genes leading to cancer [69]. Several lines of evidence correlate oxidative DNA damage, mainly associated with the normal aging process, and/or alterations in DNA repair system with neurodegeneration and cognitive impairment [70]. For these reasons, patients with genetic deficits in DNA repair systems might be subject to an increased risk to develop both cancer and neurodegenerative disorders characterized by cognitive impairment [71,72]. Regarding CICI, patients with alleles associated with less efficient DNA repair systems conceivably might be more inclined to show cognitive impairment before or after chemotherapeutic treatment.

Variations in DNA repair genes seem to be related to cancer risk; in particular, some studies reported the association between genes in the base excision repair (BER) pathway, such as 8-oxoguanine DNA glycosylase (*OGG1*) and apurinic/apyrimidinic endonuclease (*APE1/APEX1*), and risk of developing tumors [73]. Since patients with high levels of DNA damage before treatment seem to be more prone to develop cognitive impairment, polymorphisms of genes associated with low efficiency BER mechanisms have been proposed to be associated with CICI [74]. *OGG1* is a bifunctional glycosylase involved in the BER process. One of the most frequent mutagenic DNA alterations that occur during oxidative DNA damage is the formation of 8-oxoguanine (8-oxoG). OGG1, thanks to its dual lyase and glycosylase activity, removes 8-oxoG base cutting the DNA backbone [75]. OGG1 activity is present in neurons and glial cells in several CNS regions, and its levels and activity are found to be increased after neuronal injuries linked to the presence of oxidative stress, such as ischemia and reperfusion, confirming its role in repairing neuronal oxidative damage [76]. Moreover, the decreased levels of OGG1 are related to the aging process and AD [77,78]. *APEX1* gene encodes for DNA- (apurinic or apyrimidinic site) lyase. Apurinic/apyrimidinic (AP) sites are consequences of spontaneous lysis of the phosphodiester linkage, DNA damage or the excision of abnormal bases by DNA endonuclease. In the presence of oxidative stress, APEX1 is also involved in the activation of transcription factors through a redox mechanism [79]. Furthermore, increased APEX1 staining has been reported in hippocampus, surrounding temporal cortex and cerebral cortex in AD brains [80]. These studies suggest that APEX1 increases in AD in response to oxidative stress to repair oxidative DNA damage and to regulate the expression of transcriptional factors induced by oxidative stress [81]. These findings suggest that *OGG1* and *APEX1* are important to protect DNA from oxidative damage, and that a genetic deficit in those genes potentially could be linked to an increased risk to developing cognitive impairment before and after chemotherapy due to neuronal loss.

4. Telomere shortening accelerates aging and cognitive deficits after chemotherapy

Telomeres are regions of repetitive nuclear base sequences at the end of chromosomes; these sequences shorten by 20–200 base pairs during each normal DNA replication of mitotic cells. When telomeres reach a critical length, the cell undergoes senescence and apoptosis [82]. The physiological shortening of telomeres is associated with aging processes, but several factors can affect the telomere shortening processes such as genetic variation, oxidative stress, chemotherapy or neurodegenerative disorders such as AD [83,84]. Telomere length also is crucial for cancer cells. Indeed, in 80% of human cancers, the immortal phenotype of cancer cells is due to an increase in telomerase activity; telomerase is an enzyme capable to rebuild telomeres which are not active in most normal somatic cells. For this reason, emerging studies aim to develop new anti-cancer approaches focusing on the telomere shortening process and telomerase activity in cancer cells [85]. Chemotherapy directed at telomerase can lead to telomere shortening in off-target cells, in addition to its effects on cancer cells, accelerating the aging process [86]. In CNS, neuronal cells are largely post-mitotic but glial cells are subjected to the telomere shortening process [87]. The notion of the acceleration of the aging process linked to telomere shortening after chemotherapy is another proposed mechanism for CICI onset.

5. Oxidative stress and pro-inflammatory cytokines play important roles in mechanisms of CICI

Oxidative stress and correlated mitochondrial damage often occur in cancer patients or survivors after treatment of chemotherapeutic agents and are considered as one of main candidate mechanisms of CICI

[2,88]. Although some cancer patients reportedly may have high level of oxidative stress and cognitive impairment before chemotherapy, many chemotherapeutic agents are ROS-generating and are associated with DNA and protein damage in both the periphery and brain [2,3]. Immune responses follow the increase in oxidative stress, increasing pro-inflammatory cytokines locally and activate immune cells in brain. Superoxide ($O_2^-\cdot$) can increase the level of oxidative stress markers in mice plasma and activate macrophages with a large production of TNF-α after incubating plasma or macrophage culture with potassium superoxide [89]. As noted above, ROS also is an initiator of BBB disruption, triggering BBB oxidative damage, tight junction modification and matrix metalloproteinase activation [54]. Dexrazoxane, an iron chelator that can interfere with and decrease free radical formation by its putative antioxidant ability, is reportedly cardioprotective when it is administrated with Dox [90,91]. This study supports the notion that free oxidative damage is integral to CICI [2]. Protein oxidation, lipid peroxidation and dysfunctional BBB make drugs and cytokines easier to enter the brain, the organ which is more vulnerable to oxidative stress due to its high oxygen consumption rate and large presence of unsaturated fatty acid with associated labile allylic hydrogen atoms. Impaired mitochondria in brain secondary to chemotherapy-induced oxidative and nitrosative damage result in elevation of oxidative stress and eventual neuronal death, along with decreased antioxidant level and glucose dysmetabolism by inactivation of complex I [92,93]. Although not relevant to CICI directly since Dox does not cross the BBB, mitochondrial damage was found in Dox-treated neurons [94] and is associated with cognitive impairment in aging, traumatic brain injury, or neurodegenerative disorders such as PD or AD [95–97]. Accumulation of lipofuscin was also found in brain of Dox-treated mice brain along with altered autophagosomes [94].

Dox is a common anti-cancer agent for solid tumors and lymphomas, producing $O_2^-\cdot$ *via* redox cycling and leading to cardio- and neuro-toxicity. A recent study reported results of rats treated with Dox chronically at a low dose (2 mg/kg/week) [98]. In a step-through passive avoidance test, Dox led to a significantly low memory performance compared to control rats. The number of degenerative hippocampal neurons following Dox correlated with elevated apoptosis, decreased antioxidant glutathione (GSH) levels, diminished activity of catalase, and increased level of the lipid peroxidation product, malondialdehyde (MDA) in hippocampus of treated rats in the same study [98]. The cognitive impairment and associated neuronal apoptosis are ameliorated by food supplemented with astaxanthin, a carotenoid with antioxidant, anti-apoptotic and anti-inflammatory functions [98]. In another study, acute and high dose administration (25 mg/kg) of Dox increased oxidative damage indexed by protein-bound HNE and protein carbonyls (PC) in both plasma and brain of mice [99]. NOR testing revealed a cognitive impairment of mice 72 h after Dox injection. Locomotor activity was decreased by Dox even earlier, 24 h after treatment [99]. Altered neurochemical profiles in hippocampus and decreased activity of phospholipases in brain also correlated with cognitive impairment [99]. All of these deleterious changes were either completely or partially prevented by co-administration of MESNA, an antioxidant drug that scavenges free radicals [99,100]. γ-Glutamyl cysteine ethyl ester (GCEE), a precursor of the antioxidant GSH, restored GSH level and GSH transferase activity in Dox-treated mice brain equivalent to the saline-treated control group, reduced levels of all three oxidative stress markers of protein oxidation and lipid peroxidation in mice brain induced by Dox [101].

BCNU triggered ROS-dependent JNK and ERK signaling and apoptosis in neurons could be inhibited by *N*-acetyl cysteine (NAC) [102]. In addition, decreased GSH level and glutathione reductase activity were caused by BCNU [102]. NAC also protected neurons *in vitro* and rats *in vivo* from cisplatin induced oxidative stress, mitochondrial dysfunction, and/or cognitive impairment [103]. Dox generated ROS with subsequently elevated peroxisomes in neurons and mice brains [104]. Maintaining level of peroxisomes is important to regulate cellular redox homeostasis [105]. β-Cyclodextrin decreased this Dox-induced ROS production by up-regulating peroxisome-related autophagy (pexophagy) [104]. Taken together, all evidences here strongly support the notion that redox homeostasis is disrupted after many chemotherapeutic agents and that oxidative stress associated with organelle dysfunction plays an important role in CICI. That is why antioxidant supplement and co-administration of antioxidant drug are very efficient methods to moderate these damages in brain [106].

Antioxidant effectiveness in preventing oxidative damage to brain and other cellular abnormalities following chemotherapy is consistent with the notion of the role of oxidative stress associated with CICI, but this approach normally cannot be pursued in cancer therapy due, in part, to activation of glutathione-S-transferase-mediated coupling of chemotherapeutic agents to reduced GSH and subsequent removal of this complex from the cancer cell by MRP1, thereby decreasing therapeutic efficacy [107]. In contrast, antioxidants that remain and act *outside* the cancer cells do not interfere with chemotherapy, but do scavenge lipid peroxidation products in plasma, preventing inflammatory cytokines from entering the brain parenchyma [2,99,108]. Moreover, highly redox-active agents that are mitochondrial manganese superoxide dismutase (MnSOD) mimetics, brain-permeable, and selective for mitochondria show great promise of cancer cell death by exacerbating the high oxidative redox state of cancer cells to cause them to undergo apoptosis [109].

Oxidative stress mediated CICI is often accompanied by immune response and pro-inflammatory cytokine increase, including IL-1β, IL-6 and TNF-α [110,111]. IL-1β and TNF-α are important to synapse function and neural plasticity [112]. Elevated IL-6 is associated with worsening executive function and poor self-perceived cognitive disturbance in cancer patients [113,114]. CNS excitability and CICI are associated with peripheral pro-inflammatory cytokines, modulating functions of neurons and glial cells and neurotransmitter metabolism in brain [3]. DNA, synapses and neurites in neurons also were damaged after Dox treatment [36]. Chemotherapeutic agents elevate peripheral cytokine levels, which could cross the BBB, lead to immune response, and increase oxidative stress and mitochondria damage in CNS [2].

Inflammatory reactions in the CNS are related to activation of the immune cells and originate mainly from microglia [115]. Deficits in hippocampus-based memory ability and highly decreased neurogenesis in brain were found in cyclophosphamide-, cisplatin- or Dox-treated rats, with activated microglia after cyclophosphamide treatment [103,116]. The pro-inflammatory enzyme COX-2 also was upregulated with microglia activation and significant cognitive impairment in hippocampus of tumor-bearing mice treated with methotrexate [117]. Similar results of elevation of COX-2 and prostaglandin E_2 were shown in Dox-treated rat hippocampus with increased immunoactivity and glia activation, mediated by the elevated TNF-α [98]. Activation, death or any status changes of microglia conceivably could lead to more neurological inflammation and neurotoxicity [118].

Chemotherapy-induced oxidative stress-mediated TNF-α triggers iNOS production [92], thereby leading to more oxidative stress and damaged mitochondria. Activated pro-apoptotic proteins p53 and Bax, were observed in Dox-treated mice brain associated with TNF-α elevation in both the periphery and the CNS [93]. Released cytochrome *c* (cyt *c*) and increased caspase-3 activity have been found in rodent brain after chemotherapy [98,99,102]. The release of cyt *c* and initiation of apoptotic cascades lead to neuronal death in brain and we hypothesize also to cognitive impairment as consequences [2,93,99]. In a recent study, TNFKO mice were used to observe the role of TNF-α in proposed mechanisms of CICI [119]. Dox-induced oxidative stress in brains was absent in TNFKO mice. Mitochondria in brains from TNFKO mice are protected following Dox treatment, assessed by oxygen consumption rate compared to Dox-treated WT group. Choline levels in hippocampus and phospholipase D activity of the whole brain also were elevated in Dox-treated TNFKO mice compared to Dox-treated WT mice. These data provided strong evidence that TNF-α is critically associated with the

mechanisms of CICI [119].

Apolipoprotein A-I (ApoA1) is possibly one of the key factors in oxidative stress and pro-inflammatory cytokine mediated CICI. ApoA1 is part of the high density lipoprotein complex for transporting cholesterol and phospholipids to the liver for degradation. Oxidation and down-regulated expression of ApoA1 were found in a number of neurodegenerative diseases with cognitive deficits, such as AD and PD [120]. ApoA1 prevents over-production of IL-1β and TNF-α by interacting with cholesterol transport protein ABCA1 *via* the JAK2/STAT3 pathway or inhibiting interaction of monocytes and T-cells [121]. However, ApoA1 is oxidized by Dox with a con-committent increased TNF-α level and oxidative stress in plasma of cancer patients [108]. This result of oxidized ApoA1 correlating with Dox-induced TNF-α elevation also was shown with mice in the same study, and oxidized ApoA1 lost the ability to inhibit TNF-α production in LPS-treated macrophage culture [108]. The results are consistent with previous discussion in this section of this review that ROS-associated chemotherapy leads to oxidized proteins in the periphery, with subsequent stimulations to pro-inflammatory cytokines in the periphery that transport to the CNS.

6. Neuronal genetic predisposition and CICI

Previous studies show that only a subset of cancer survivors exhibit a long term cognitive impairment after chemotherapy. For this reason, neuronal genetic predisposition has been proposed as a potential risk factor for CICI. Disruption of dopamine and serotonin levels also has been associated with cognitive dysfunction [122].

Single nucleotide polymorphisms (SNP) of apolipoprotein E (*APOE*), brain-derived neurotrophic factor (*BDNF*) and catechol-*O*-methyltransferase (*COMT*) genes reportedly are involved in neurocognitive functioning and aging associated with CICI of breast cancer survivors [123]. The *APOE* gene encodes for APOE protein, which, combining with lipids, forms lipoproteins responsible for cholesterol transport in blood circulation. The allele variant *APOE e4* is known to be correlated to normal cognitive decline and aging and is one of the main genetic risk factors for AD [124]. Moreover, in breast, testicular and lymphoma cancer survivors, carriers of the e4 allele of *APOE* gene, showed reduced visual memory, spatial ability, and psychomotor functions after chemotherapy [125]. Other studies of breast cancer survivors correlated a reduced hippocampal volume to the *APOE e4* allele, consistent with reduced memory functioning [126].

BDNF is a neurotrophin widely expressed in CNS, mostly present in hippocampus and cerebral cortex. BDNF is involved in neuronal repair, dendritic and axonal growth, long-term potentiation and synaptic plasticity [127], associated with hippocampal volume reduction and memory function in aging processes [128]. Moreover, the *BDNF* Val66Met mutation has been shown to be associated with CICI and might be linked with cognitive depression associated with inflammation in breast cancer survivors [129,130]. In addition, this BDNF mutation has also been associated with lower hippocampal volume and poorer performance in measures of memory [131–133]. Early-stage breast cancer patients with *BDNF Met* allele who have received chemotherapy were more likely to be protected from CICI with better performance on verbal fluency and multitasking test, compared to those patients with a *BDNF Val* allele [134]. A longitudinal study also showed plasma BDNF levels were reduced after chemotherapy associated with self-reported cognitive impairment, however, no significant changes of plasma BDNF levels were observed after chemotherapy in patients with BDNF Met/Met genotype [135].

The *COMT* gene encodes the protein catechol-*O*-methyltransferase, an enzyme that catalyzes the *O*-methylation of the catecholamines (dopamine, epinephrine, and norepinephrine), regulating their degradation. Polymorphism of the *COMT* gene has been linked with cognitive impairment associated with chemotherapy. Dopamine is an important neurotransmitter involved in executive and memory function in the frontal cortex, and COMT is the main modulator of dopamine levels in this area (In PD, the substantia nigra pars compacta is the major brain region demonstrating pathology). *COMT* gene polymorphisms have been associated with memory performance in normal aging and with different prefrontal function and structure [136]. In particular, the Val158Met polymorphism has been shown to affect neurotransmission, decreasing dopamine availability [137]. Furthermore, *COMT* polymorphism has been correlated with cognitive impairment in lymphocytic leukemia [138] and in adult breast cancer survivors [139]. In both cases, patients with the *COMT-Val* allele exhibited decreased performance in attention, motor speed, and verbal fluency when compared to patients with the *COMT-Met* allele.

7. Changes of hormone levels after chemotherapy involved in CICI mechanisms

Low levels of hormones, such as estrogen, progesterone and testosterone, influence cognitive function and have complicated neuroprotective and antioxidant effects as well as deleterious effects on cognition [140–145]. Estrogen receptors are abundant in brain areas associated with memory and cognition [146]. Several studies show that these hormones, beside the neurotrophic and protective effects, are involved also in speech and memory functions [147]. Moreover, estrogen has a role in maintaining telomere lengths and it affects cognitive function by influencing the brain cholinergic system [148,149]. The physiological reduction of estrogen levels, associated with menopause in women, has been related to cognitive deficits, particularly in memory functioning [142]. This is relevant in the chemotherapy-induced cognitive impairment context because chemotherapy also can induce early menopause in women [150]. However, a cautionary note is apropos here: in a clinical trial of long-term estrogen alone or combined with progestin therapy for postmenopausal women, loss of cognitive function was observed [145]. In addition to the effects of chemotherapy, other adjuvant treatments, such as tamoxifen and aromatase inhibitors used in breast cancer or androgen ablation in prostate tumor, can lower levels of hormones [151–154]. Inhibitors of enzymes involving estrogen generating or agents that block estrogen receptors are commonly used in treatment for breast cancer. Reportedly, verbal memory of breast cancer patients treated with anti-estrogen therapy was impaired [155]. Because of their role on cognitive function, the alteration of hormone levels after chemotherapy is considered as a plausible contributing factor in the mechanisms for development of CICI.

8. Conclusion

With the large and increasing number of cancer survivors in the world, such people are seeking a longer and good quality of life. CICI is subtle with loss of learning ability, memory, attention, executive function and processing speed, and these conditions can be long-lasting or short-term, affecting the quality of life of cancer survivors. Patients are eager to recover a normal life not only physically, but also mentally. That this condition is so debilitating necessitates, in our opinion, that urgent investigations into the biochemical mechanisms of CICI , ranging from the effects of anti-cancer drugs, prevention and protection of patients from cognitive deficits, and other side effects. Based on the discussion in this review, it is impossible to attribute CICI to a single mechanism or simple candidate protein, molecule or gene. Multiple pathogenic mechanisms most likely are involved. The cross-talk and interaction among all possible candidates erect a complicated network of processes that lead to eventual neuronal apoptosis and cognitive deficits in many cancer survivors. Altered brain structures, decreased neural plasticity and telomere shortening could be contributing to the observed long term cognitive dysfunction. Brain resident DNA damage, hormone changes and gene polymorphism also likely contribute to CICI. Neural inflammation and oxidative damage to key proteins, lipids,

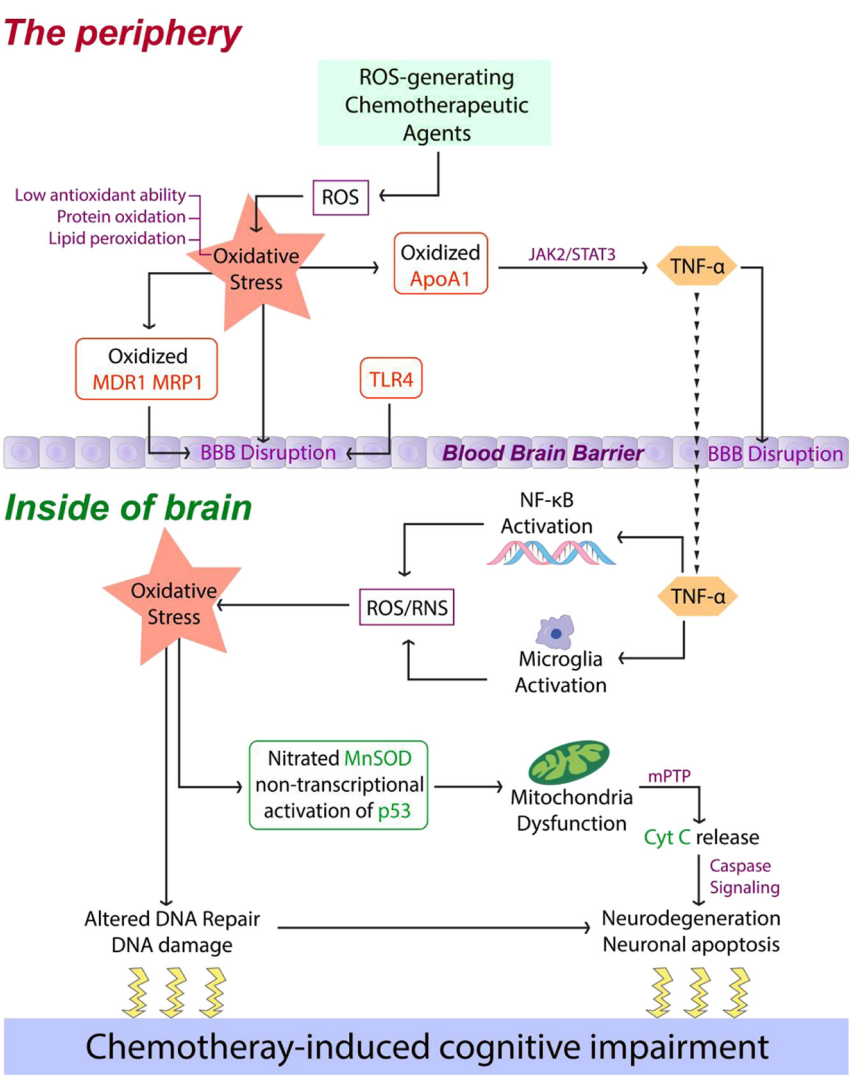

Fig. 2. Proposed mechanisms of CICI mediated by ROS-generating chemotherapeutic drugs and associated oxidative stress. Such anti-cancer drugs in the periphery trigger oxidative stress and result in protein oxidation and lipid peroxidation, producing elevated TNF-α that crosses the BBB by receptor-mediated endocytosis or by oxidative stress-mediated disruption of the BBB (see [2,56]). TLR4 activation leads to BBB disruption and production of cytokines such as TNF-α. Once TNF-α goes into brain, local immune response is triggered by microglia activation and NF-κB activation, triggering ROS/RNS leading to oxidative stress. DNA repair systems are affected by the oxidative stress in brain and lead to neurodegeneration. Impaired mitochondria function follows the nitration of MnSOD and p53 non-transcriptional activation. As a result, mitochondria permeability transition pore (mPTP) is opened. Cyt *c* released from the pore initiates caspase signaling, leading to neural apoptosis. Once neurodegeneration and neuronal death happen, cognitive deficits of chemotherapy-treated cancer survivors appear.

DNA and membranes are considered to be fundamental phenomena underlying CICI mechanisms, potentially leading to other contributors to CICI. Anti-cancer drugs could produce oxidative stress in the periphery, cause protein oxidation, lipid peroxidation, DNA damage and telomere shortening, and increase the permeability of BBB to pro-inflammatory cytokines. We propose that key pro-inflammatory cytokines, including TNF-α, that are elevated in the periphery by ROS associated chemotherapeutic drugs, cross the BBB, to lead to subsequent neuronal death, particularly in the hippocampus and pre-frontal cortex. These changes result in the clinical presentation of CICI. After increased oxidative stress in the periphery leading to events described above, elevation of TNF-α-mediated oxidative stress, inflammatory cytokines and mitochondrial damage are found in brain. Subsequent opening of the mitochondrial permeability transition pore leads to release cyt *c* to activate apoptotic pathways. Therefore, we hypothesize that CICI results secondary to apoptosis of neurons in brain (Fig. 2.). Continued studies of CICI in preclinical and clinical settings are necessary to narrow the list of potential mechanistic players noted in this review and determine their likely interactions that cause this serious loss of quality of life of cancer survivors. Such studies are ongoing in our laboratories.

Transparency document

The Transparency document associated with this article can be found, in online version.

Acknowledgements

This work was supported in part by a Multiple PI R01 grant from the National Cancer Institute [1 R01 CA217934-02 to D.A.B., D.S.C., and S.B.].

References

[1] W. Miller, R.L. Siegel, C.C. Lin, A.B. Mariotto, J.L. Kramer, J.H. Rowland, K.D. Stein, R. Alteri, A. Jemal, Cancer treatment and survivorship statistics, 2016, CA Cancer J. Clin. 66 (2016) 271–289, https://doi.org/10.3322/caac.21349.

[2] D.A. Butterfield, The 2013 SFRBM discovery award: selected discoveries from the butterfield laboratory of oxidative stress and its sequela in brain in cognitive disorders exemplified by Alzheimer disease and chemotherapy induced cognitive impairment, Free Radic. Biol. Med. 74 (2014) 157–174, https://doi.org/10.1016/j.freeradbiomed.2014.06.006.

[3] T.A. Ahles, A.J. Saykin, Candidate mechanisms for chemotherapy-induced cognitive changes, Nat. Rev. Cancer 7 (2007) 192–201, https://doi.org/10.1038/nrc2073.

[4] K. Hermelink, Chemotherapy and cognitive function in breast cancer patients: the so-called chemo brain, J. Natl. Cancer Inst. Monogr. 2015 (2015) 67–69, https://doi.org/10.1093/jncimonographs/lgv009.

[5] H.C.F. Moore, An overview of chemotherapy-related cognitive dysfunction, or "chemobrain", Oncology (Williston Park) 28 (2014) 797–804.

[6] C.D. Runowicz, C.R. Leach, N.L. Henry, K.S. Henry, H.T. Mackey, R.L. Cowens-Alvarado, R.S. Cannady, M.L. Pratt-Chapman, S.B. Edge, L.A. Jacobs, A. Hurria, L.B. Marks, S.J. LaMonte, E. Warner, G.H. Lyman, P.A. Ganz, American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline, CA Cancer J. Clin. 66 (2016) 43–73, https://doi.org/10.3322/caac.21319.

[7] S.M. Castellino, N.J. Ullrich, M.J. Whelen, B.J. Lange, Developing interventions for

cancer-related cognitive dysfunction in childhood cancer survivors, J. Natl. Cancer Inst. 106 (2014), https://doi.org/10.1093/jnci/dju186.
[8] P. Jean-Pierre, P.C. Winters, T.A. Ahles, M. Antoni, F.D. Armstrong, F. Penedo, S.E. Lipshultz, T.L. Miller, K. Fiscella, Prevalence of self-reported memory problems in adult cancer survivors: a national cross-sectional study, J. Oncol. Pract. 8 (2012) 30–34, https://doi.org/10.1200/JOP.2011.000231.
[9] J.S. Wefel, A.K. Saleeba, A.U. Buzdar, C.A. Meyers, Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer, Cancer 116 (2010) 3348–3356, https://doi.org/10.1002/cncr.25098.
[10] V. Koppelmans, M.M.B. Breteler, W. Boogerd, C. Seynaeve, C. Gundy, S.B. Schagen, Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 30 (2012) 1080–1086, https://doi.org/10.1200/JCO.2011.37.0189.
[11] J. Debess, J.Ø. Riis, M.C. Engebjerg, M. Ewertz, Cognitive function after adjuvant treatment for early breast cancer: a population-based longitudinal study, Breast Cancer Res. Treat. 121 (2010) 91–100, https://doi.org/10.1007/s10549-010-0756-8.
[12] M. Vitali, C.I. Ripamonti, F. Roila, C. Proto, D. Signorelli, M. Imbimbo, G. Corrao, A. Brissa, G. Rosaria, F. de Braud, M.C. Garassino, G. Lo Russo, Cognitive impairment and chemotherapy: a brief overview, Crit. Rev. Oncol. Hematol. 118 (2017) 7–14, https://doi.org/10.1016/j.critrevonc.2017.08.001.
[13] H.C.F. Moore, M.W. Parsons, G.H. Yue, L.A. Rybicki, W. Siemionow, Electroencephalogram power changes as a correlate of chemotherapy-associated fatigue and cognitive dysfunction, Support. Care Cancer 22 (2014) 2127–2131, https://doi.org/10.1007/s00520-014-2197-0.
[14] Y. Chen, P. Jungsuwadee, M. Vore, D.A. Butterfield, D.K. St. Clair, Collateral damage in cancer chemotherapy: oxidative stress in nontargeted tissues, Mol. Interv. 7 (2007) 147–156, https://doi.org/10.1124/mi.7.3.6.
[15] S.R. Kesler, C.L. Watson, D.W. Blayney, Brain network alterations and vulnerability to simulated neurodegeneration in breast cancer, Neurobiol. Aging 36 (2015) 2429–2442, https://doi.org/10.1016/j.neurobiolaging.2015.04.015.
[16] J.S. Wefel, S.R. Kesler, K.R. Noll, S.B. Schagen, Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults, CA Cancer J. Clin. 65 (2015) 123–138, https://doi.org/10.3322/caac.21258.
[17] S.R. Kesler, Default mode network as a potential biomarker of chemotherapy-related brain injury, Neurobiol. Aging 35 (Suppl. 2) (2014) S11–S19, https://doi.org/10.1016/j.neurobiolaging.2014.03.036.
[18] S.R. Kesler, D.W. Blayney, Neurotoxic effects of anthracycline- vs non-anthracycline-based chemotherapy on cognition in breast cancer survivors, JAMA Oncol. 2 (2016) 185–192, https://doi.org/10.1001/jamaoncol.2015.4333.
[19] S. Deprez, F. Amant, A. Smeets, R. Peeters, A. Leemans, W. Van Hecke, J.S. Verhoeven, M.-R. Christiaens, J. Vandenberghe, M. Vandenbulcke, S. Sunaert, Longitudinal assessment of chemotherapy-induced structural changes in cerebral white matter and its correlation with impaired cognitive functioning, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 30 (2012) 274–281, https://doi.org/10.1200/JCO.2011.36.8571.
[20] B.C. McDonald, S.K. Conroy, T.A. Ahles, J.D. West, A.J. Saykin, Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study, Breast Cancer Res. Treat. 123 (2010) 819–828, https://doi.org/10.1007/s10549-010-1088-4.
[21] S.K. Conroy, B.C. McDonald, D.J. Smith, L.R. Moser, J.D. West, L.M. Kamendulis, J.E. Klaunig, V.L. Champion, F.W. Unverzagt, A.J. Saykin, Alterations in brain structure and function in breast cancer survivors: effect of post-chemotherapy interval and relation to oxidative DNA damage, Breast Cancer Res. Treat. 137 (2013) 493–502, https://doi.org/10.1007/s10549-012-2385-x.
[22] B.C. McDonald, S.K. Conroy, D.J. Smith, J.D. West, A.J. Saykin, Frontal gray matter reduction after breast cancer chemotherapy and association with executive symptoms: a replication and extension study, Brain Behav. Immun. 30 (2013) S117–S125, https://doi.org/10.1016/j.bbi.2012.05.007 (Suppl).
[23] R.B. Raffa, Is a picture worth a thousand (forgotten) words?: neuroimaging evidence for the cognitive deficits in 'chemo-fog'/'chemo-brain', J. Clin. Pharm. Ther. 35 (2010) 1–9, https://doi.org/10.1111/j.1365-2710.2009.01044.x.
[24] R.L. Barry, N.E. Byun, M.N. Tantawy, C.A. Mackey, G.H. Wilson, A.J. Stark, M.P. Flom, L.C. Gee, C.C. Quarles, In vivo neuroimaging and behavioral correlates in a rat model of chemotherapy-induced cognitive dysfunction, Brain Imaging Behav. 12 (2018) 87–95, https://doi.org/10.1007/s11682-017-9674-2.
[25] T.R. Groves, R. Farris, J.E. Anderson, T.C. Alexander, F. Kiffer, G. Carter, J. Wang, M. Boerma, A.R. Allen, 5-Fluorouracil chemotherapy upregulates cytokines and alters hippocampal dendritic complexity in aged mice, Behav. Brain Res. 316 (2017) 215–224, https://doi.org/10.1016/j.bbr.2016.08.039.
[26] B.E. Lee, B.Y. Choi, D.K. Hong, J.H. Kim, S.H. Lee, A.R. Kho, H. Kim, H.C. Choi, S.W. Suh, The cancer chemotherapeutic agent paclitaxel (Taxol) reduces hippocampal neurogenesis via down-regulation of vesicular zinc, Sci. Rep. 7 (2017) 11667, , https://doi.org/10.1038/s41598-017-12054-7.
[27] H. Cheng, W. Li, L. Gong, H. Xuan, Z. Huang, H. Zhao, L.S. Wang, K. Wang, Altered resting-state hippocampal functional networks associated with chemotherapy-induced prospective memory impairment in breast cancer survivors, Sci. Rep. 7 (2017) 45135, , https://doi.org/10.1038/srep45135.
[28] J. Dietrich, M. Prust, J. Kaiser, Chemotherapy, cognitive impairment and hippocampal toxicity, Neuroscience 309 (2015) 224–232, https://doi.org/10.1016/j.neuroscience.2015.06.016.
[29] R.J. Ferguson, B.C. McDonald, A.J. Saykin, T.A. Ahles, Brain structure and function differences in monozygotic twins: possible effects of breast cancer chemotherapy, J. Clin. Oncol. 25 (2007) 3866–3870, https://doi.org/10.1200/JCO.2007.10.8639.
[30] P.A. Reuter-Lorenz, B. Cimprich, Cognitive function and breast cancer: promise and potential insights from functional brain imaging, Breast Cancer Res. Treat. 137 (2013) 33–43, https://doi.org/10.1007/s10549-012-2266-3.
[31] P.A. Ganz, L. Kwan, S.A. Castellon, A. Oppenheim, J.E. Bower, D.H.S. Silverman, S.W. Cole, M.R. Irwin, S. Ancoli-Israel, T.R. Belin, Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance, J. Natl. Cancer Inst. 105 (2013) 791–801, https://doi.org/10.1093/jnci/djt073.
[32] B. Baudino, F. D'agata, P. Caroppo, G. Castellano, S. Cauda, M. Manfredi, E. Geda, L. Castelli, P. Mortara, L. Orsi, F. Cauda, K. Sacco, R.B. Ardito, L. Pinessi, G. Geminiani, R. Torta, G. Bisi, The chemotherapy long-term effect on cognitive functions and brain metabolism in lymphoma patients, Q. J. Nucl. Med. Mol. Imaging 56 (2012) 559–568.
[33] P. Karschnia, M.W. Parsons, J. Dietrich, Pharmacologic management of cognitive impairment induced by cancer therapy, Lancet Oncol. 20 (2019) e92–e102, https://doi.org/10.1016/S1470-2045(18)30938-0.
[34] M.C. Janelsins, C.E. Heckler, L.J. Peppone, C. Kamen, K.M. Mustian, S.G. Mohile, A. Magnuson, I.R. Kleckner, J.J. Guido, K.L. Young, A.K. Conlin, L.R. Weiselberg, J.W. Mitchell, C.A. Ambrosone, T.A. Ahles, G.R. Morrow, 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. Off. J. Am. Soc. Clin. Oncol. 35 (2017) 506–514, https://doi.org/10.1200/JCO.2016.68.5826.
[35] T.A. Ahles, A.J. Saykin, B.C. McDonald, C.T. Furstenberg, B.F. Cole, B.S. Hanscom, T.J. Mulrooney, G.N. Schwartz, P.A. Kaufman, Cognitive function in breast cancer patients prior to adjuvant treatment, Breast Cancer Res. Treat. 110 (2008) 143–152, https://doi.org/10.1007/s10549-007-9686-5.
[36] J.F.M. Manchon, Y. Dabaghian, N.-E. Uzor, S.R. Kesler, J.S. Wefel, A.S. Tsvetkov, Levetiracetam mitigates doxorubicin-induced DNA and synaptic damage in neurons, Sci. Rep. 6 (2016) 25705, , https://doi.org/10.1038/srep25705.
[37] R.-Y. Liu, Y. Zhang, B.L. Coughlin, L.J. Cleary, J.H. Byrne, Doxorubicin attenuates serotonin-induced long-term synaptic facilitation by phosphorylation of p38 mitogen-activated protein kinase, J. Neurosci. 34 (2014) 13289–13300, https://doi.org/10.1523/JNEUROSCI.0538-14.2014.
[38] J. Avila, M. Llorens-Martín, N. Pallas-Bazarra, M. Bolós, J.R. Perea, A. Rodríguez-Matellán, F. Hernández, Cognitive decline in neuronal aging and Alzheimer's disease: role of NMDA receptors and associated proteins, Front. Neurosci. 11 (2017), https://doi.org/10.3389/fnins.2017.00626.
[39] K.R. Walker, G. Tesco, Molecular mechanisms of cognitive dysfunction following traumatic brain injury, Front. Aging Neurosci. 5 (2013), https://doi.org/10.3389/fnagi.2013.00029.
[40] P.D. Cole, V. Vijayanathan, N.F. Ali, M.E. Wagshul, E.J. Tanenbaum, J. Price, V. Dalal, M.E. Gulinello, Memantine protects rats treated with intrathecal methotrexate from developing spatial memory deficits, Clin. Cancer Res. 19 (2013) 4446–4454, https://doi.org/10.1158/1078-0432.CCR-13-1179.
[41] V. Vijayanathan, M. Gulinello, N. Ali, P.D. Cole, Persistent cognitive deficits, induced by intrathecal methotrexate, are associated with elevated CSF concentrations of excitotoxic glutamate analogs and can be reversed by an NMDA antagonist, Behav. Brain Res. 225 (2011) 491–497, https://doi.org/10.1016/j.bbr.2011.08.006.
[42] R.A. Drachtman, P.D. Cole, C.B. Golden, S.J. James, S. Melnyk, J. Aisner, B.A. Kamen, Dextromethorphan is effective in the treatment of subacute methotrexate neurotoxicity, Pediatr. Hematol. Oncol. 19 (2002) 319–327, https://doi.org/10.1080/08880010290057336.
[43] P.M. Haddad, S.M. Dursun, Neurological complications of psychiatric drugs: clinical features and management, Hum. Psychopharmacol. 23 (Suppl. 1) (2008) 15–26, https://doi.org/10.1002/hup.918.
[44] R. Seigers, S.B. Schagen, O. Van Tellingen, J. Dietrich, Chemotherapy-related cognitive dysfunction: current animal studies and future directions, Brain Imaging Behav. 7 (2013) 453–459, https://doi.org/10.1007/s11682-013-9250-3.
[45] J. Dietrich, R. Han, Y. Yang, M. Mayer-Pröschel, M. Noble, CNS progenitor cells and oligodendrocytes are targets of chemotherapeutic agents in vitro and in vivo, J. Biol. 5 (2006) 22, https://doi.org/10.1186/jbiol50.
[46] H.R. Wardill, R.J. Gibson, Y.Z.A.V. Sebille, K.R. Secombe, J.K. Coller, I.A. White, J. Manavis, M.R. Hutchinson, V. Staikopoulos, R.M. Logan, J.M. Bowen, Irinotecan-induced gastrointestinal dysfunction and pain are mediated by common TLR4-dependent mechanisms, Mol. Cancer Ther. 15 (2016) 1376–1386, https://doi.org/10.1158/1535-7163.MCT-15-0990.
[47] W.A. Banks, From blood–brain barrier to blood–brain interface: new opportunities for CNS drug delivery, Nat. Rev. Drug Discov. 15 (2016) 275–292, https://doi.org/10.1038/nrd.2015.21.
[48] H.E. de Vries, G. Kooij, D. Frenkel, S. Georgopoulos, A. Monsonego, D. Janigro, Inflammatory events at blood–brain barrier in neuroinflammatory and neurodegenerative disorders: implications for clinical disease, Epilepsia 53 (2012) 45–52, https://doi.org/10.1111/j.1528-1167.2012.03702.x.
[49] M.A. Erickson, W.A. Banks, Blood–brain barrier dysfunction as a cause and consequence of Alzheimer's disease, J. Cereb. Blood Flow Metab. 33 (2013) 1500–1513, https://doi.org/10.1038/jcbfm.2013.135.
[50] S.Y. Kim, M. Buckwalter, H. Soreq, A. Vezzani, D. Kaufer, Blood–brain barrier dysfunction–induced inflammatory signaling in brain pathology and epileptogenesis, Epilepsia 53 (2012) 37–44, https://doi.org/10.1111/j.1528-1167.2012.03701.x.
[51] S. Tabaczar, J. Czepas, A. Koceva-Chyla, E. Kilanczyk, J. Piasecka-Zelga, K. Gwozdzinski, The effect of the nitroxide pirolin on oxidative stress induced by doxorubicin and taxanes in the rat brain, J. Physiol. Pharmacol. 68 (2017) 295–308.

[52] H.R. Wardill, K.A. Mander, Y.Z.A.V. Sebille, R.J. Gibson, R.M. Logan, J.M. Bowen, S.T. Sonis, Cytokine-mediated blood brain barrier disruption as a conduit for cancer/chemotherapy-associated neurotoxicity and cognitive dysfunction, Int. J. Cancer 139 (2016) 2635–2645, https://doi.org/10.1002/ijc.30252.
[53] J.E. Fardell, J. Zhang, R. De Souza, J. Vardy, I. Johnston, C. Allen, J. Henderson, M. Piquette-Miller, The impact of sustained and intermittent docetaxel chemotherapy regimens on cognition and neural morphology in healthy mice, Psychopharmacology 231 (2014) 841–852, https://doi.org/10.1007/s00213-013-3301-8.
[54] P.B.L. Pun, J. Lu, S. Moochhala, Involvement of ROS in BBB dysfunction, Free Radic. Res. 43 (2009) 348–364, https://doi.org/10.1080/10715760902751902.
[55] W. Pan, A.J. Kastin, Interactions of cytokines with the blood-brain barrier: implications for feeding, Curr. Pharm. Des. 9 (2003) 827–831.
[56] W.A. Banks, M.A. Erickson, The blood–brain barrier and immune function and dysfunction, Neurobiol. Dis. 37 (2010) 26–32, https://doi.org/10.1016/j.nbd.2009.07.031.
[57] C. Vaure, Y. Liu, A comparative review of toll-like receptor 4 expression and functionality in different animal species, Front. Immunol. 5 (2014), https://doi.org/10.3389/fimmu.2014.00316.
[58] P. Jungsuwadee, M.P. Cole, R. Sultana, G. Joshi, J. Tangpong, D.A. Butterfield, D.K.S. Clair, M. Vore, Increase in Mrp1 expression and 4-hydroxy-2-nonenal adduction in heart tissue of Adriamycin-treated C57BL/6 mice, Mol. Cancer Ther. 5 (2006) 2851–2860, https://doi.org/10.1158/1535-7163.MCT-06-0297.
[59] G. Joshi, R. Sultana, J. Tangpong, M.P. Cole, D.K. St Clair, M. Vore, S. Estus, D.A. Butterfield, Free radical mediated oxidative stress and toxic side effects in brain induced by the anti cancer drug adriamycin: insight into chemobrain, Free Radic. Res. 39 (2005) 1147–1154, https://doi.org/10.1080/10715760500143478.
[60] Y. Zhou, G. Zhang, Z. Rao, Y. Yang, Q. Zhou, H. Qin, Y. Wei, X. Wu, Increased brain uptake of venlafaxine loaded solid lipid nanoparticles by overcoming the efflux function and expression of P-gp, Arch. Pharm. Res. 38 (2015) 1325–1335, https://doi.org/10.1007/s12272-014-0539-6.
[61] R.W. Robey, K.M. Pluchino, M.D. Hall, A.T. Fojo, S.E. Bates, M.M. Gottesman, Revisiting the role of ABC transporters in multidrug-resistant cancer, Nat. Rev. Cancer 18 (2018) 452–464, https://doi.org/10.1038/s41568-018-0005-8.
[62] K.O. Alfarouk, C.-M. Stock, S. Taylor, M. Walsh, A.K. Muddathir, D. Verduzco, A.H.H. Bashir, O.Y. Mohammed, G.O. Elhassan, S. Harguindey, S.J. Reshkin, M.E. Ibrahim, C. Rauch, Resistance to cancer chemotherapy: failure in drug response from ADME to P-gp, Cancer Cell Int. 15 (2015), https://doi.org/10.1186/s12935-015-0221-1.
[63] N.M. Mhaidat, O.Y. Alshogran, O.F. Khabour, K.H. Alzoubi, I.I. Matalka, W.J. Haddadin, I.O. Mahasneh, A.N. Aldaher, Multi-drug resistance 1 genetic polymorphism and prediction of chemotherapy response in Hodgkin's Lymphoma, J. Exp. Clin. Cancer Res. 30 (2011) 68, , https://doi.org/10.1186/1756-9966-30-68.
[64] T. Muramatsu, D.R. Johnson, R.A. Finch, L.K. Johnson, J.J. Leffert, Z.P. Lin, G. Pizzorno, A.C. Sartorelli, Age-related differences in vincristine toxicity and biodistribution in wild-type and transporter-deficient mice, Oncol. Res. 14 (2004) 331–343.
[65] A. Galaup, A. Paci, Pharmacology of dimethanesulfonate alkylating agents: busulfan and treosulfan, Expert Opin. Drug Metab. Toxicol. 9 (2013) 333–347, https://doi.org/10.1517/17425255.2013.737319.
[66] S. Puyo, D. Montaudon, P. Pourquier, From old alkylating agents to new minor groove binders, Crit. Rev. Oncol. Hematol. 89 (2014) 43–61, https://doi.org/10.1016/j.critrevonc.2013.07.006.
[67] M.L. Fishel, M.R. Vasko, M.R. Kelley, DNA repair in neurons: so if they don't divide what's to repair? Mutat. Res. 614 (2007) 24–36, https://doi.org/10.1016/j.mrfmmm.2006.06.007.
[68] M.I. Turan, A. Cayir, N. Cetin, H. Suleyman, I. Siltelioglu Turan, H. Tan, An investigation of the effect of thiamine pyrophosphate on cisplatin-induced oxidative stress and DNA damage in rat brain tissue compared with thiamine: thiamine and thiamine pyrophosphate effects on cisplatin neurotoxicity, Hum. Exp. Toxicol. 33 (2014) 14–21, https://doi.org/10.1177/0960327113485251.
[69] D.E. Barnes, T. Lindahl, Repair and genetic consequences of endogenous DNA base damage in mammalian cells, Annu. Rev. Genet. 38 (2004) 445–476, https://doi.org/10.1146/annurev.genet.38.072902.092448.
[70] D.K. Jeppesen, V.A. Bohr, T. Stevnsner, DNA repair deficiency in neurodegeneration, Prog. Neurobiol. 94 (2011) 166–200, https://doi.org/10.1016/j.pneurobio.2011.04.013.
[71] E.L. Goode, C.M. Ulrich, J.D. Potter, Polymorphisms in DNA repair genes and associations with cancer risk, Cancer Epidemiol. Biomark. Prev. 11 (2002) 1513–1530.
[72] R.L. Rolig, P.J. McKinnon, Linking DNA damage and neurodegeneration, Trends Neurosci. 23 (2000) 417–424.
[73] R.J. Hung, J. Hall, P. Brennan, P. Boffetta, Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review, Am. J. Epidemiol. 162 (2005) 925–942, https://doi.org/10.1093/aje/kwi318.
[74] A.A. Argyriou, K. Assimakopoulos, G. Iconomou, F. Giannakopoulou, H.P. Kalofonos, Either called "chemobrain" or "chemofog", the long-term chemotherapy-induced cognitive decline in cancer survivors is real, J. Pain Symptom Manage. 41 (2011) 126–139.
[75] H. Ide, M. Kotera, Human DNA glycosylases involved in the repair of oxidatively damaged DNA, Biol. Pharm. Bull. 27 (2004) 480–485.
[76] T. Verjat, A. Dhénaut, J.P. Radicella, S. Araneda, Detection of 8-oxoG DNA glycosylase activity and OGG1 transcripts in the rat CNS, Mutat. Res. 460 (2000) 127–138.
[77] F. Cardozo-Pelaez, M. Sanchez-Contreras, A.B.C. Nevin, Ogg1 null mice exhibit age-associated loss of the nigrostriatal pathway and increased sensitivity to MPTP, Neurochem. Int. 61 (2012) 721–730, https://doi.org/10.1016/j.neuint.2012.06.013.
[78] M.S. Lillenes, A. Rabano, M. Støen, T. Riaz, D. Misaghian, L. Møllersen, Y. Esbensen, C.-C. Günther, P. Selnes, V.T.V. Stenset, T. Fladby, T. Tønjum, Altered DNA base excision repair profile in brain tissue and blood in Alzheimer's disease, Mol. Brain 9 (2016) 61, , https://doi.org/10.1186/s13041-016-0237-z.
[79] A.M. Whitaker, T.S. Flynn, B.D. Freudenthal, Molecular snapshots of APE1 proofreading mismatches and removing DNA damage, Nat. Commun. 9 (2018) 399, , https://doi.org/10.1038/s41467-017-02175-y.
[80] Z. Tan, N. Sun, S.S. Schreiber, Immunohistochemical localization of redox factor-1 (Ref-1) in Alzheimer's hippocampus, Neuroreport 9 (1998) 2749–2752.
[81] A. Sliwinska, P. Sitarek, M. Toma, P. Czarny, E. Synowiec, R. Krupa, P. Wigner, K. Bialek, D. Kwiatkowski, A. Korycinska, I. Majsterek, J. Szemraj, P. Galecki, T. Sliwinski, Decreased expression level of BER genes in Alzheimer's disease patients is not derivative of their DNA methylation status, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 79 (2017) 311–316, https://doi.org/10.1016/j.pnpbp.2017.07.010.
[82] Z. Zhao, X. Pan, L. Liu, N. Liu, Telomere length maintenance, shortening, and lengthening, J. Cell. Physiol. 229 (2014) 1323–1329, https://doi.org/10.1002/jcp.24537.
[83] C.P. Schröder, G.B. Wisman, S. de Jong, W.T. van der Graaf, M.H. Ruiters, N.H. Mulder, L.F. de Leij, A.G. van der Zee, E.G. de Vries, Telomere length in breast cancer patients before and after chemotherapy with or without stem cell transplantation, Br. J. Cancer 84 (2001) 1348–1353, https://doi.org/10.1054/bjoc.2001.1803.
[84] M. Vasa-Nicotera, S. Brouilette, M. Mangino, J.R. Thompson, P. Braund, J.-R. Clemitson, A. Mason, C.L. Bodycote, S.M. Raleigh, E. Louis, N.J. Samani, Mapping of a major locus that determines telomere length in humans, Am. J. Hum. Genet. 76 (2005) 147–151, https://doi.org/10.1086/426734.
[85] S. Sengupta, M. Sobo, K. Lee, S. Senthil Kumar, A.R. White, I. Mender, C. Fuller, L.M.L. Chow, M. Fouladi, J.W. Shay, R. Drissi, Induced telomere damage to treat telomerase expressing therapy-resistant pediatric brain tumors, Mol. Cancer Ther. 17 (2018) 1504–1514, https://doi.org/10.1158/1535-7163.MCT-17-0792.
[86] A.D. Bolzán, M.S. Bianchi, DNA and chromosome damage induced by bleomycin in mammalian cells: an update, Mutat. Res. 775 (2018) 51–62, https://doi.org/10.1016/j.mrrev.2018.02.003.
[87] B.E. Flanary, W.J. Streit, Progressive telomere shortening occurs in cultured rat microglia, but not astrocytes, Glia 45 (2004) 75–88, https://doi.org/10.1002/glia.10301.
[88] A.M. Gaman, A. Uzoni, A. Popa-Wagner, A. Andrei, E.-B. Petcu, The role of oxidative stress in etiopathogenesis of chemotherapy induced cognitive impairment (CICI)-"chemobrain", Aging Dis. 7 (2016) 307–317, https://doi.org/10.14336/AD.2015.1022.
[89] J.T.R. Keeney, S. Miriyala, T. Noel, J.A. Moscow, D.K. St Clair, D.A. Butterfield, Superoxide induces protein oxidation in plasma and TNF-α elevation in macrophage culture: insights into mechanisms of neurotoxicity following doxorubicin chemotherapy, Cancer Lett. 367 (2015) 157–161, https://doi.org/10.1016/j.canlet.2015.07.023.
[90] Z. Junjing, Z. Yan, Z. Baolu, Scavenging effects of dexrazoxane on free radicals, J. Clin. Biochem. Nutr. 47 (2010) 238–245, https://doi.org/10.3164/jcbn.10-64.
[91] N. Bansal, S.M. Amdani, K.K. Hutchins, S.E. Lipshultz, Cardiovascular disease in survivors of childhood cancer, Curr. Opin. Pediatr. 30 (2018) 628–638, https://doi.org/10.1097/MOP.0000000000000675.
[92] J. Tangpong, M.P. Cole, R. Sultana, S. Estus, M. Vore, W. St. Clair, S. Ratanachaiyavong, D.K. St. Clair, D.A. Butterfield, Adriamycin-mediated nitration of manganese superoxide dismutase in the central nervous system: insight into the mechanism of chemobrain, J. Neurochem. 100 (2007) 191–201, https://doi.org/10.1111/j.1471-4159.2006.04179.x.
[93] J. Tangpong, M.P. Cole, R. Sultana, G. Joshi, S. Estus, M. Vore, W. St. Clair, S. Ratanachaiyavong, D.K. St. Clair, D.A. Butterfield, Adriamycin-induced, TNF-α-mediated central nervous system toxicity, Neurobiol. Dis. 23 (2006) 127–139, https://doi.org/10.1016/j.nbd.2006.02.013.
[94] J.F. Moruno-Manchon, N.-E. Uzor, S.R. Kesler, J.S. Wefel, D.M. Townley, A.S. Nagaraja, S. Pradeep, L.S. Mangala, A.K. Sood, A.S. Tsvetkov, TFEB ameliorates the impairment of the autophagy-lysosome pathway in neurons induced by doxorubicin, Aging 8 (2016) 3507–3519, https://doi.org/10.18632/aging.101144.
[95] R.K. Chaturvedi, M. Flint Beal, Mitochondrial diseases of the brain, Free Radic. Biol. Med. 63 (2013) 1–29, https://doi.org/10.1016/j.freeradbiomed.2013.03.018.
[96] J. Liu, E. Head, A.M. Gharib, W. Yuan, R.T. Ingersoll, T.M. Hagen, C.W. Cotman, B.N. Ames, Memory loss in old rats is associated with brain mitochondrial decay and RNA/DNA oxidation: partial reversal by feeding acetyl-L-carnitine and/or R-alpha-lipoic acid, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 2356–2361, https://doi.org/10.1073/pnas.261709299.
[97] A. Sauerbeck, J. Gao, R. Readnower, M. Liu, J.R. Pauly, G. Bing, P.G. Sullivan, Pioglitazone attenuates mitochondrial dysfunction, cognitive impairment, cortical tissue loss, and inflammation following traumatic brain injury, Exp. Neurol. 227 (2011) 128–135, https://doi.org/10.1016/j.expneurol.2010.10.003.
[98] S.E. El-Agamy, A.K. Abdel-Aziz, S. Wahdan, A. Esmat, S.S. Azab, Astaxanthin ameliorates doxorubicin-induced cognitive impairment (chemobrain) in experimental rat model: impact on oxidative, inflammatory, and apoptotic machineries, Mol. Neurobiol. 55 (2018) 5727–5740, https://doi.org/10.1007/s12035-017-0797-7.

[99] J.T.R. Keeney, X. Ren, G. Warrier, T. Noel, D.K. Powell, J.M. Brelsfoard, R. Sultana, K.E. Saatman, D.K.S. Clair, D.A. Butterfield, J.T.R. Keeney, X. Ren, G. Warrier, T. Noel, D.K. Powell, J.M. Brelsfoard, R. Sultana, K.E. Saatman, D.K. St. Clair, D.A. Butterfield, Doxorubicin-induced elevated oxidative stress and neurochemical alterations in brain and cognitive decline: protection by MESNA and insights into mechanisms of chemotherapy-induced cognitive impairment ("chemobrain"), Oncotarget 9 (2018) 30324–30339, https://doi.org/10.18632/oncotarget.25718.

[100] J. Hayslip, E.V. Dressler, H. Weiss, T.J. Taylor, M. Chambers, T. Noel, S. Miriyala, J.T.R. Keeney, X. Ren, R. Sultana, M. Vore, D.A. Butterfield, D.S. Clair, J.A. Moscow, Plasma TNF-α and soluble TNF receptor levels after doxorubicin with or without co-administration of MESNA—a randomized, cross-over clinical study, PLoS ONE 10 (2015) e0124988, , https://doi.org/10.1371/journal.pone.0124988.

[101] G. Joshi, S. Hardas, R. Sultana, D.K.S. Clair, M. Vore, D.A. Butterfield, Glutathione elevation by γ-glutamyl cysteine ethyl ester as a potential therapeutic strategy for preventing oxidative stress in brain mediated by in vivo administration of adriamycin: implication for chemobrain, J. Neurosci. Res. 85 (2007) 497–503, https://doi.org/10.1002/jnr.21158.

[102] J.M. An, S.S. Kim, J.H. Rhie, D.M. Shin, S.R. Seo, J.T. Seo, Carmustine induces ERK- and JNK-dependent cell death of neuronally-differentiated PC12 cells via generation of reactive oxygen species, Toxicol. in Vitro 25 (2011) 1359–1365, https://doi.org/10.1016/j.tiv.2011.05.006.

[103] N. Lomeli, K. Di, J. Czerniawski, J.F. Guzowski, D.A. Bota, Cisplatin-induced mitochondrial dysfunction is associated with impaired cognitive function in rats, Free Radic. Biol. Med. 102 (2017) 274–286, https://doi.org/10.1016/j.freeradbiomed.2016.11.046.

[104] J.F. Moruno-Manchon, N.-E. Uzor, S.R. Kesler, J.S. Wefel, D.M. Townley, A.S. Nagaraja, S. Pradeep, L.S. Mangala, A.K. Sood, A.S. Tsvetkov, Peroxisomes contribute to oxidative stress in neurons during doxorubicin-based chemotherapy, Mol. Cell. Neurosci. 86 (2018) 65–71, https://doi.org/10.1016/j.mcn.2017.11.014.

[105] D. Trompier, A. Vejux, A. Zarrouk, C. Gondcaille, F. Geillon, T. Nury, S. Savary, G. Lizard, Brain peroxisomes, Biochimie 98 (2014) 102–110, https://doi.org/10.1016/j.biochi.2013.09.009.

[106] G. Joshi, C.D. Aluise, M.P. Cole, R. Sultana, M. Vore, D.K. St Clair, D.A. Butterfield, Alterations in brain antioxidant enzymes and redox proteomic identification of oxidized brain proteins induced by the anti-cancer drug adriamycin: implications for oxidative stress-mediated chemobrain, Neuroscience 166 (2010) 796–807, https://doi.org/10.1016/j.neuroscience.2010.01.021.

[107] P. Jungsuwadee, R. Nithipongvanitch, Y. Chen, T.D. Oberley, D.A. Butterfield, D.K.S. Clair, M. Vore, Mrp1 localization and function in cardiac mitochondria after doxorubicin, Mol. Pharmacol. 75 (2009) 1117–1126, https://doi.org/10.1124/mol.108.052209.

[108] C.D. Aluise, S. Miriyala, T. Noel, R. Sultana, P. Jungsuwadee, T.J. Taylor, J. Cai, W.M. Pierce, M. Vore, J.A. Moscow, D.K. St Clair, D.A. Butterfield, 2-Mercaptoethane sulfonate prevents doxorubicin-induced plasma protein oxidation and TNF-α release: implications for the reactive oxygen species-mediated mechanisms of chemobrain, Free Radic. Biol. Med. 50 (2011) 1630–1638, https://doi.org/10.1016/j.freeradbiomed.2011.03.009.

[109] L. Chaiswing, W.H. St. Clair, D.K. St. Clair, Redox paradox: a novel approach to therapeutics-resistant cancer, Antioxid. Redox Signal. 29 (2018) 1237–1272, https://doi.org/10.1089/ars.2017.7485.

[110] N. Groven, E.A. Fors, V.C. Iversen, L.R. White, S.K. Reitan, Association between cytokines and psychiatric symptoms in chronic fatigue syndrome and healthy controls, Nord. J. Psychiatry (2018) 1–5, https://doi.org/10.1080/08039488.2018.1493747.

[111] D.-D. Shi, Y.-H. Huang, C.S.W. Lai, C.M. Dong, L.C. Ho, E.X. Wu, Q. Li, X.-M. Wang, S.K. Chung, P.C. Sham, Z.-J. Zhang, Chemotherapy-induced cognitive impairment is associated with cytokine dysregulation and disruptions in neuroplasticity, Mol. Neurobiol. (2018), https://doi.org/10.1007/s12035-018-1224-4.

[112] F.R. Rizzo, A. Musella, F. De Vito, D. Fresegna, S. Bullitta, V. Vanni, L. Guadalupi, M. Stampanoni Bassi, F. Buttari, G. Mandolesi, D. Centonze, A. Gentile, Tumor necrosis factor and interleukin-1β modulate synaptic plasticity during neuroinflammation, Neural Plast. (2018), https://doi.org/10.1155/2018/8430123.

[113] P.C. Trask, P. Esper, M. Riba, B. Redman, Psychiatric side effects of interferon therapy: prevalence, proposed mechanisms, and future directions, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 18 (2000) 2316–2326, https://doi.org/10.1200/JCO.2000.18.11.2316.

[114] Y.T. Cheung, T. Ng, M. Shwe, H.K. Ho, K.M. Foo, M.T. Cham, J.A. Lee, G. Fan, Y.P. Tan, W.S. Yong, P. Madhukumar, S.K. Loo, S.F. Ang, M. Wong, W.Y. Chay, W.S. Ooi, R.A. Dent, Y.S. Yap, R. Ng, A. Chan, Association of proinflammatory cytokines and chemotherapy-associated cognitive impairment in breast cancer patients: a multi-centered, prospective, cohort study, Ann. Oncol. 26 (2015) 1446–1451, https://doi.org/10.1093/annonc/mdv206.

[115] R.M. Ransohoff, V.H. Perry, Microglial physiology: unique stimuli, specialized responses, Annu. Rev. Immunol. 27 (2009) 119–145, https://doi.org/10.1146/annurev.immunol.021908.132528.

[116] L.-A. Christie, M.M. Acharya, V.K. Parihar, A. Nguyen, V. Martirosian, C.L. Limoli, Impaired cognitive function and hippocampal neurogenesis following cancer chemotherapy, Clin. Cancer Res. 18 (2012) 1954–1965, https://doi.org/10.1158/1078-0432.CCR-11-2000.

[117] M. Yang, J.-S. Kim, J. Kim, S. Jang, S.-H. Kim, J.-C. Kim, T. Shin, H. Wang, C. Moon, Acute treatment with methotrexate induces hippocampal dysfunction in a mouse model of breast cancer, Brain Res. Bull. 89 (2012) 50–56, https://doi.org/10.1016/j.brainresbull.2012.07.003.

[118] J.C. Santos, L.M. Pyter, Neuroimmunology of behavioral comorbidities associated with cancer and cancer treatments, Front. Immunol. 9 (2018), https://doi.org/10.3389/fimmu.2018.01195.

[119] X. Ren, J.T.R. Keeney, S. Miriyala, T. Noel, D.K. Powell, L. Chaiswing, S. Bondada, D.K. St Clair, D.A. Butterfield, 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 (2018) 1–8, https://doi.org/10.1016/j.freeradbiomed.2018.12.029.

[120] J.T.R. Keeney, A.M. Swomley, S. Förster, J.L. Harris, R. Sultana, D.A. Butterfield, Apolipoprotein A-I: insights from redox proteomics for its role in neurodegeneration, PROTEOMICS – Clin. Appl. 7 (2013) 109–122, https://doi.org/10.1002/prca.201200087.

[121] X. Ren, D.K. St. Clair, D.A. Butterfield, Dysregulation of cytokine mediated chemotherapy induced cognitive impairment, Pharmacol. Res. 117 (2017) 267–273, https://doi.org/10.1016/j.phrs.2017.01.001.

[122] C.J. Wilson, C.E. Finch, H.J. Cohen, Cytokines and cognition–the case for a head-to-toe inflammatory paradigm, J. Am. Geriatr. Soc. 50 (2002) 2041–2056.

[123] H. Cheng, W. Li, C. Gan, B. Zhang, Q. Jia, K. Wang, The COMT (rs165599) gene polymorphism contributes to chemotherapy-induced cognitive impairment in breast cancer patients, Am. J. Transl. Res. 8 (2016) 5087–5097.

[124] R.M. Koffie, T. Hashimoto, H.-C. Tai, K.R. Kay, A. Serrano-Pozo, D. Joyner, S. Hou, K.J. Kopeikina, M.P. Frosch, V.M. Lee, D.M. Holtzman, B.T. Hyman, T.L. Spires-Jones, Apolipoprotein E4 effects in Alzheimer's disease are mediated by synaptotoxic oligomeric amyloid-β, Brain J. Neurol. 135 (2012) 2155–2168, https://doi.org/10.1093/brain/aws127.

[125] T.A. Ahles, A.J. Saykin, W.W. Noll, C.T. Furstenberg, S. Guerin, B. Cole, L.A. Mott, The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy, Psychooncology 12 (2003) 612–619, https://doi.org/10.1002/pon.742.

[126] S. Kesler, M. Janelsins, D. Koovakkattu, O. Palesh, K. Mustian, G. Morrow, F.S. Dhabhar, Reduced hippocampal volume and verbal memory performance associated with interleukin-6 and tumor necrosis factor-alpha levels in chemotherapy-treated breast cancer survivors, Brain Behav. Immun. 30 (2013) S109–S116, https://doi.org/10.1016/j.bbi.2012.05.017 (Suppl).

[127] J. Savitz, M. Solms, R. Ramesar, The molecular genetics of cognition: dopamine, COMT and BDNF, Genes Brain Behav. 5 (2006) 311–328, https://doi.org/10.1111/j.1601-183X.2005.00163.x.

[128] K.I. Erickson, R.S. Prakash, M.W. Voss, L. Chaddock, S. Heo, M. McLaren, B.D. Pence, S.A. Martin, V.J. Vieira, J.A. Woods, E. McAuley, A.F. Kramer, Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume, J. Neurosci. 30 (2010) 5368–5375, https://doi.org/10.1523/JNEUROSCI.6251-09.2010.

[129] L.N. Dooley, P.A. Ganz, S.W. Cole, C.M. Crespi, J.E. Bower, Val66Met BDNF polymorphism as a vulnerability factor for inflammation-associated depressive symptoms in women with breast cancer, J. Affect. Disord. 197 (2016) 43–50, https://doi.org/10.1016/j.jad.2016.02.059.

[130] T. Ng, S.M.J. Teo, H.L.A. Yeo, M. Shwe, Y.X. Gan, Y.T. Cheung, Y.P. Tan, W.S. Yong, P. Madhukumar, K.W.-J. Loh, S.-L. Koo, A. Jain, G.E. Lee, M. Wong, R.A. Dent, Y.S. Yap, R.C.H. Ng, C.C. Khor, H.K. Ho, A. Chan, Evaluation of brain-derived neurotrophic factor (BDNF) genetic polymorphism (rs6265) on chemotherapy-associated cognitive impairment in early-stage breast cancer (ESBC) patients, J. Clin. Oncol. 33 (2015) 9616, https://doi.org/10.1200/jco.2015.33.15_suppl.9616.

[131] M.F. Egan, M. Kojima, J.H. Callicott, T.E. Goldberg, B.S. Kolachana, A. Bertolino, E. Zaitsev, B. Gold, D. Goldman, M. Dean, B. Lu, D.R. Weinberger, The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function, Cell 112 (2003) 257–269.

[132] L. Pezawas, B.A. Verchinski, V.S. Mattay, J.H. Callicott, B.S. Kolachana, R.E. Straub, M.F. Egan, A. Meyer-Lindenberg, D.R. Weinberger, The brain-derived neurotrophic factor val66met polymorphism and variation in human cortical morphology, J. Neurosci. 24 (2004) 10099–10102, https://doi.org/10.1523/JNEUROSCI.2680-04.2004.

[133] A. Mallei, A. Ieraci, S. Corna, D. Tardito, F.S. Lee, M. Popoli, Global epigenetic analysis of BDNF Val66Met mice hippocampus reveals changes in dendrite and spine remodeling genes, Hippocampus (2018), https://doi.org/10.1002/hipo.22991.

[134] T. Ng, S.M. Teo, H.L. Yeo, M. Shwe, Y.X. Gan, Y.T. Cheung, K.M. Foo, M.T. Cham, J.A. Lee, Y.P. Tan, G. Fan, W.S. Yong, M. Preetha, W.-J.K. Loh, S.-L. Koo, A. Jain, G.E. Lee, M. Wong, R. Dent, Y.S. Yap, R. Ng, C.C. Khor, H.K. Ho, A. Chan, Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer, Neuro Oncol. 18 (2016) 244–251, https://doi.org/10.1093/neuonc/nov162.

[135] T. Ng, Y.Y. Lee, J. Chae, A.H.L. Yeo, M. Shwe, Y.X. Gan, R.C.H. Ng, P.P.Y. Chu, C.C. Khor, H.K. Ho, A. Chan, Evaluation of plasma brain-derived neurotrophic factor levels and self-perceived cognitive impairment post-chemotherapy: a longitudinal study, BMC Cancer 17 (2017), https://doi.org/10.1186/s12885-017-3861-9.

[136] P. Bastos, T. Gomes, L. Ribeiro, Catechol-O-methyltransferase (COMT): an update on its role in cancer, neurological and cardiovascular diseases, Rev. Physiol. Biochem. Pharmacol. 173 (2017) 1–39, https://doi.org/10.1007/112_2017_2.

[137] K.W. Miskowiak, H.L. Kjaerstad, M.M. Støttrup, A.M. Svendsen, K.M. Demant, L.K. Hoeffding, T.M. Werge, K.E. Burdick, K. Domschke, A.F. Carvalho, E. Vieta, M. Vinberg, L.V. Kessing, H.R. Siebner, J. Macoveanu, The catechol-O-

methyltransferase (COMT) Val158Met genotype modulates working memory-related dorsolateral prefrontal response and performance in bipolar disorder, Bipolar Disord. 19 (2017) 214–224, https://doi.org/10.1111/bdi.12497.
[138] P.D. Cole, Y. Finkelstein, K.E. Stevenson, T.M. Blonquist, V. Vijayanathan, L.B. Silverman, D.S. Neuberg, S.E. Sallan, P. Robaey, D.P. Waber, Polymorphisms in genes related to oxidative stress are associated with inferior cognitive function after therapy for childhood acute lymphoblastic leukemia, J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 33 (2015) 2205–2211, https://doi.org/10.1200/JCO.2014.59.0273.
[139] B.J. Small, K.S. Rawson, E. Walsh, H.S.L. Jim, T.F. Hughes, L. Iser, M.A. Andrykowski, P.B. Jacobsen, Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors, Cancer 117 (2011) 1369–1376, https://doi.org/10.1002/cncr.25685.
[140] C. Behl, Oestrogen as a neuroprotective hormone, Nat. Rev. Neurosci. 3 (2002) 433–442, https://doi.org/10.1038/nrn846.
[141] M. Białek, P. Zaremba, K.K. Borowicz, S.J. Czuczwar, Neuroprotective role of testosterone in the nervous system, Pol. J. Pharmacol. 56 (2004) 509–518.
[142] L. Kocoska-Maras, A.F. Rådestad, K. Carlström, T. Bäckström, B. von Schoultz, A.L. Hirschberg, Cognitive function in association with sex hormones in postmenopausal women, Gynecol. Endocrinol. 29 (2013) 59–62, https://doi.org/10.3109/09513590.2012.705385.
[143] P.M. Maki, E. Sundermann, Hormone therapy and cognitive function, Hum. Reprod. Update 15 (2009) 667–681, https://doi.org/10.1093/humupd/dmp022.
[144] V.W. Henderson, Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause, J. Steroid Biochem. Mol. Biol. 142 (2014) 99–106, https://doi.org/10.1016/j.jsbmb.2013.05.010.
[145] J.H. Kang, J. Weuve, F. Grodstein, Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women, Neurology 63 (2004) 101–107.
[146] V. Shilling, V. Jenkins, L. Fallowfield, T. Howell, The effects of hormone therapy on cognition in breast cancer, J. Steroid Biochem. Mol. Biol. 86 (2003) 405–412.
[147] J. Liu, H. Lin, Y. Huang, Y. Liu, B. Wang, F. Su, Cognitive effects of long-term dydrogesterone treatment used alone or with estrogen on rat menopausal models of different ages, Neuroscience 290 (2015) 103–114, https://doi.org/10.1016/j.neuroscience.2015.01.042.
[148] J. Lin, C.H. Kroenke, E. Epel, H.A. Kenna, O.M. Wolkowitz, E. Blackburn, N.L. Rasgon, Greater endogenous estrogen exposure is associated with longer telomeres in postmenopausal women at risk for cognitive decline, Brain Res. 1379 (2011) 224–231, https://doi.org/10.1016/j.brainres.2010.10.033.
[149] P. Newhouse, J. Dumas, Estrogen-cholinergic interactions: implications for cognitive aging, Horm. Behav. 74 (2015) 173–185, https://doi.org/10.1016/j.yhbeh.2015.06.022.
[150] V. Tiong, A.M. Rozita, N.A. Taib, C.H. Yip, C.H. Ng, Incidence of chemotherapy-induced ovarian failure in premenopausal women undergoing chemotherapy for breast cancer, World J. Surg. 38 (2014) 2288–2296, https://doi.org/10.1007/s00268-014-2542-y.
[151] F.P. Downie, H.G. Mar Fan, N. Houédé-Tchen, Q. Yi, I.F. Tannock, Cognitive function, fatigue, and menopausal symptoms in breast cancer patients receiving adjuvant chemotherapy: evaluation with patient interview after formal assessment, Psychooncology 15 (2006) 921–930, https://doi.org/10.1002/pon.1035.
[152] K. Paraska, C.M. Bender, Cognitive dysfunction following adjuvant chemotherapy for breast cancer: two case studies, Oncol. Nurs. Forum 30 (2003) 473–478, https://doi.org/10.1188/03.ONF.473-478.
[153] V.A. Jenkins, D.J. Bloomfield, V.M. Shilling, T.L. Edginton, Does neoadjuvant hormone therapy for early prostate cancer affect cognition? Results from a pilot study, BJU Int. 96 (2005) 48–53, https://doi.org/10.1111/j.1464-410X.2005.05565.x.
[154] H.L. McGinty, K.M. Phillips, H.S.L. Jim, J.M. Cessna, Y. Asvat, M.G. Cases, B.J. Small, P.B. Jacobsen, Cognitive functioning in men receiving androgen deprivation therapy for prostate cancer: a systematic review and meta-analysis, Support. Care Cancer 22 (2014) 2271–2280, https://doi.org/10.1007/s00520-014-2285-1.
[155] C.M. Schilder, C. Seynaeve, L.V. Beex, W. Boogerd, S.C. Linn, C.M. Gundy, H.M. Huizenga, J.W. Nortier, Effects of tamoxifen and exemestane on cognitive functioning of postmenopausal patients with breast cancer: results from the neuropsychological side study of the tamoxifen and exemestane adjuvant multinational trial, J. Clin. Oncol. 28 (2010) 1294–1300.