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Invited Review-pharmacology across disciplines

Dysregulation of cytokine mediated chemotherapy induced cognitive impairment

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ABSTRACT

One of the major complaints patients who survive cancer often make is chemotherapy induced cognitive impairment (CICI), which survivors often call "chemo brain." CICI is a side effect of chemotherapy due to the cytotoxicity and neurotoxicity of anti-cancer drugs causing structural and functional changes in brain, even when drugs that do not cross the blood brain barrier (BBB) are used. Diminished cognitive functions including diminution of learning and memory, concentration and attention, processing speed and executive functions that reduce quality of life and ability to work are common signs and symptoms of CICI. There still is not a clarified and complete mechanism for CICI, but researchers have pointed to several biochemical candidates. Chemotherapy-induced, cytokine-mediated involvement in CICI will be mainly discussed in this review paper with emphasis on different types of cytokines, correlated with BBB and epigenetic changes. Mechanisms of ROS-generating, anti-cancer drugs and their relation to cytokine-mediated CICI will be emphasized.

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1. Introduction

Chemotherapy induced cognitive impairment (CICI), also called "chemofog" or "chemo brain," is a detriment to the quality of life of a large fraction of the approximately 14 million cancer survivors in the USA [1]. Studies suggested that anti-cancer drugs cause a peripheral inflammatory response leading to structural and functional brain changes [2,3], resulting in neuropsychological deficits and cognitive impairments [4,5]. These changes could be subtle or severe; of short duration or sustained for years; appearing during or after using antineoplastic agents, causing reduced brain functions including executive ability, working memory, attention and processing speed [1,3,5–8].

Although some researchers also found that cognitive impairment may happen before the start of chemotherapy [9,10], it is still worthy to study CICI. Patients who survived cancers may still suffer from poor quality of life due to slow reactions, disabilities in multitasking, diminished memory ability, and other symptoms. Survivors may or may not be able to recover to normal life with families and friends or regular working tasks. Thus, understand-

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ing of mechanisms and etiology of CICI are urgently needed since human beings are living longer and cancer survivors are seeking a high quality of life not mere survival.

There is still much to learn to obtain a clarified pathogenesis for CICI. So far, several candidate mechanisms have been hypothesized to cause cognitive changes after chemotherapy, including: genetic deficits; DNA damage stress and shorter telomere length; blood brain barrier integrity; reduced hormone level; and immunoinflammatory and cytokine dysregulation [5,11,12]. These reasons could cause CICI directly or indirectly, acting either singly or in concert, and lead to neuronal death with cognitive dysfunction as a consequence.

In this review paper, cytokine dysregulation will be primarily discussed because recent studies showed notably that chemotherapy induced cytokine changes are associated with drugs that generate ROS/RNS in the periphery, leading ultimately to brain structural and functional damage and cognitive impairments [1,13–16]. Clinical studies have suggested an association between levels of inflammatory cytokines and chemotherapeutic drugs [17,18]. Also, cancer per se can induce changes in cytokine levels [19], but obvious increased complaints starting after chemotherapy suggest a correlation of chemotherapy and both subjective reports and objective tests of brain dysfunction. The cytokine regulation system involves numerous members, and levels of cytokines change rapidly. These complications make it difficult to investigate cytokine-mediated CICI.

Cytokines play important roles in cell signaling to regulate immune and inflammatory response, initiating or mediating several peripheral and neuronal cascades. Cytokines also are involved in metabolism of neurotransmitters like dopamine and serotonin as well as neuronal repair and modulation of neurons or glia cells [5]. Changes of cytokine levels in the periphery of cancer patients can be caused by multiple factors. Macrophages release pro-inflammatory cytokines in response to cancer or cancer treatment and lead to stimulated immune responses. Psychological and physical stress [20] of patients due to diagnosis of cancer, long term treatments and various factors [8] also are proposed to cause disturbance of cytokine levels. In addition, chemotherapy-caused death of cells of both tumor and normal tissue could trigger alterations of cytokine levels [8]. Tumor metastasis also involves secreting cytokines from cancer cells to surrounding tissues [21]. The multiple factors mentioned above could affect cytokine levels, requiring delicate experimental design and considerations for different situations.

Homeostatic systems will respond to inflammatory cytokines in the periphery associated with illness including cognitive impairment by mechanisms to provide beneficial conditions for survival [22]. Chemotherapeutic drugs induced cytokine changes occur rapidly in CICI to deliver information and messages of any small changes *in vivo* circumstances. However, alterations of epigenetic modifications, on the other hand, occur in response to cytokine elevation and last long and lead to significant structural and functional changes in brain [8].

1.1. Blood brain barrier and cytokine-induced CICI

The BBB is composed of tightly joined endothelial cells that prevent toxins in the peripheral system from entering the brain. Many current chemotherapeutic agents usually cannot penetrate the BBB unless special circumstances arise [23–25]. However, chemotherapy induced pro-inflammatory cytokines such as interlukin-1 (IL-1), interlukin-6 (IL-6) and tumor necrosis factor-alpha (TNFalpha) are able to cross the BBB from the peripheral immune system to the central nervous system (CNS) [26] and evoke local inflammatory responses in brain [25,27–29]. Cytokines cross the BBB by passive diffusion through leaky regions [30] or more commonly by receptor-mediated endocytosis [31].

Learning tasks are affected negatively in multiple areas such as hippocampus and prefrontal cortex by cytotoxic chemotherapeutic drugs [32–34]. Meanwhile, cytotoxicity of drugs and the following inflammation responses may change the structure and integrity of BBB and furthermore make it easy for inflammatory cytokines in tightly the periphery or even cancer drugs to the across BBB [16], amplifying the cytokine responses and neurotoxicity in brain and leading to brain structural changes, among which are decreased volumes of white [35–37] and gray [38] matter and hippocampus [39]. Cytokines also are deleterious to the tight junctions of the BBB [40] causing partial breaking down of the BBB. Extracellular components, adhesion molecules and tight junction were predicted to be altered and disrupted by TNFalpha and IL-1beta induced gut toxicity [40]. Once anti-cancer drugs enter brain, they could reduce the density of dendritic spines and lead to shortening of dendritic branch points, complexity and length [13]. All of the mentioned brain structure changes could contribute to neurotoxicity and neuronal apoptosis and resultant cognitive impairments.

1.2. Cytokines and CICI

Cytokines and chemokines are small signaling proteins that can be produced by immune cells. Tumor necrosis factors and various interleukins are the two main types of cytokines produced by antigen-presenting cells in the peripheral immune system [41,42] and predominately by glia in brain [13]. Increased pro-inflammatory cytokines including IL-1, IL-6 and TNFalpha of immune response are associated with decreased ability to learn, impaired working memory and gradual cognitive decline of elderly people [43–47]. Meanwhile, cytokine treatments, including TNFalpha and IL-2, are correlated with depression and other cognitive impairments in the studies with cytokine treated cancer patients [48,49]. The implications of chemotherapy induced cytokine mediated cognitive impairment include the need for further studies.

One consequence of cytokine dysregulation after chemotherapy, epigenetic changes without affecting genetic sequences may occur [50], which leads to long-term alterations of brain and sustained CICI for years after cessation of anti-cancer drugs [8]. Epigenetic alterations were proposed as a response to indirect chemotherapy induced inflammation or directly to chemotherapy and may lead to cellular signal changes and telomere shortening [51]. Enhancer of zeste 2 (EZH2) is an important DNA repair enzyme [52] that was hypothesized to initiate several epigenetic modifications including DNA methylation and resulting chromosomal instability [51]. Lyon et al. postulated that chemotherapy induced cytokine mediated epigenetic changes may affect EZH2-mediated chromosomal instability with telomere shortening, leading to cell death or abnormal gene expression, with CICI as a final consequence [51]. In the same study, only breast cancer patients who developed sustained neuropsychological deficits after chemotherapy had transient methylation for a subset of genes [51]. Another animal study displayed an association of impaired learning and memory with increased histone H3 acetylation and decreased histone deacetylase activity in hippocampus [53]. More studies are required to investigate relationships among epigenetic changes and chemotherapy induced cytokine alterations to advance research to develop a mechanism of CICI. Conceivably, biomarkers resulting from such studies could monitor efficacy of chemotherapeutic approaches to prevent CICI.

1.3. Interleukin and cytokine-mediated CICI

IL-1beta plays important roles in regulation of immune response and inflammation. Release of IL-1beta from immune cells is first

through macrophage stimulation by peripheral cytotoxicity, damaged cells and tissues, and other deleterious messages induced by chemotherapeutic drugs or cancer via the toll-like receptors located on the macrophage surface [54]. NF-κB transcription factor, JNK and P38 MAPK are then activated to generate IL-1beta inactive precursor, Pro-IL-1beta [34]. Oligomeric NLPR3 inflammasome, composed of NLPR3 protein and pro-CASP-1 via CARD homotypic interaction or the linkage of CARD containing adaptor protein such as ASC or PyCard, is then recruited to activate mature IL-1beta [55]. Some anti-cancer drugs, for example doxorubicin (Dox), can trigger the P38 MAPK/JNK pathway directly through an upstream kinase of the MAPK cascade without involvement of toll-like receptors [56,57]. Furthermore, doxorubicin plays a role in facilitating formation of the NLPR3 inflammasome, promoting release of activated IL-1beta [57] and triggering cytokine-mediated processes.

IL-beta also was shown in hippocampus, a locus of memory processing. Hippocampal and hypothalamic function may be altered. The plasma IL-1beta transported to CNS would then stimulate local IL-1beta in hippocampus, changing cognitive and mood processes [7].

A large study demonstrating associations between cytokines and chemotherapy induced cognitive impairment was published recently [58]. Ninety-nine patients who had been diagnosed with early stage breast cancer were recruited within twelve weeks of diagnosis. The patients were then treated with chemotherapeutic regimens of either doxorubicin or docetaxel with cyclophosphamide. The results showed associations between higher plasma IL-1beta and poorer response speed, increased IL-6 and greater self-perceived cognitive disturbances, elevated IL-4 and improved response speed and cognitive functions. These results are consistent with the notion that IL-1beta may be a potential biomarker for mild cognitive impairment prior to development of Alzheimer's Disease (AD) and also consistent with the concept that IL-4 may be involved in neuroprotective pathways to increase executive functions and learning [58,59]. Memory and learning function were facilitated in IL-6 KO mice, which also suggested that increased IL-6 after chemotherapy is correlated to the cognitive impairment, In particular, the passive avoidance test showed the possible interaction between IL6 and the cholinergic system [60]. Dysregulated cytokine levels in brain may have influence on neurotransmitter systems and altered integrity and plasticity of neurons, bringing direct influence of cognitive dysregulation and neurodegenerations[8]. It is conceivable that abnormal cholinergic neurotransmitters also could play a role in chemotherapy induced cognitive impairment.

1.4. TNFalpha and cytokine-mediated CICI

A study involving ninety-three women with breast cancer through neuropsychological tests, self-reports and cytokines analysis in blood sample of patients after chemotherapy was conducted [23]. Soluble TNF receptor II (sTNF-RII) levels were shown to be elevated in plasma of patients treated with chemotherapy. Higher concentrations of sTNF-RII were associated with increased self-reported forgetfulness. PET scan results showed less brain metabolism in the frontal cortex that correlated with higher sTNF-RII levels within three months after chemotherapy. Patients who reported fewer complaints of memory had lower sTNF-RII 12 months after chemotherapy. Taken together, the authors suggested an important role for TNFalpha in CICI.

Dox is a commonly used chemotherapeutic agent for leukemia and solid tumors, generating reactive oxidative species (ROS) in the periphery via redox cycling [3,61]. A number of studies showed chemotherapy induced tissue injuries via ROS, including damaged mitochondrial functions in brain, an organ with a relatively high oxygen tension. Dox also is correlated to brain structural changes and cognitive impairment in several clinical and animal studies although Dox, as noted above, cannot cross the BBB. Oxidative damage in brain was examined following i.p. injection of Dox to mice, and all three of biomarkers of oxidative stress were elevated significantly, including protein oxidation [indexed by protein carbonyl and 3-nitrotyrosine (3-NT)] and lipid peroxidation [indexed by protein-bound 4-hydroxynonenal (HNE)] [11]. GSH levels and the ratio of GSH/GSSH were significant lower in brain of Dox-treated mice than the saline groups [62], demonstrating loss of levels of this important antioxidant by chemotherapy.

To develop the linkage between drugs unable to cross the BBB and oxidative stress and damage in brain, Tangpong et al. [63] detected the elevation of the chemotherapy induced mediator cytokine, TNFalpha in both plasma and brain. These researches first proved that Dox cannot penetrate the BBB, but did concentrate at the choroid plexus. Dox-treated mice showed significantly increased TNFalpha in both plasma and hippocampal and cortical areas with a diminished brain mitochondrial respiration rate indicating damaged brain mitochondria [28,64]. Intraperitoneal injection of Dox also lead to translocation of p53 and Bax to mitochondria and higher level of antiapoptotic protein Bcl-xL. Furthermore, Dox-induced release of cytochrome c and elevated caspase 3 in this study were consistent with neuronal apoptosis, also confirmed by TUNEL staining [63]. All of above-mentioned changes caused by Dox in this study could be counteracted or alleviated by co-administration of anti-TNFalpha antibody to the rodents. This finding suggests that peripheral TNFalpha is the source of elevated TNFalpha in brain. Moreover, brain-localized TNFalpha causes new TNF production. We postulate that this elevated TNFalpha in brain is a critical component of the mechanism of CICI.

NF-κB is a redox-sensitive nuclear transcription factor, and the NF-κB activation cascade is triggered by certain initiators, including peripheral TNFalpha transport to brain via TNF receptor I endocytosis [65]. TNFalpha and iNOS are the downstream products of activation of the NF-κB pathway [66,67]. Activated NF-κB translocates into nucleus and induces iNOS expression [68,69] and further transcriptional activation of TNFalpha gene [70,71]. NO, the product of iNOS, initiates protein nitration and further activation of NF-κB [72].

To validate that TNFalpha triggers mitochondrial dysfunction and apoptotic neuronal death, iNOS KO mice were employed in another study to investigate TNFalpha mediated brain mitochondria dysfunctions [64]. The authors demonstrated that injection of TNFalpha or Dox can produce iNOS message in brain of WT mice, which is prevented by co-administration of anti-TNFalpha antibody. Dysfunction of mitochondria (revealed by low respiration control ratio), nitrated MnSOD and decreased activity of MnSOD in brain were shown in Dox treated WT mice, but all of these deleterious changes were abrogated in iNOSKO mice [64].

1.5. ApoA1 and cytokine mediated mechanism of CICI

High density lipoproteins (HDL) are involved in inflammatory regulation and cholesterol metabolism and are protective against atherosclerosis of humans [73]. Apolipoprotein A-I (ApoA1) is a component of HDL to transfer cholesterol and phospholipids from tissues to liver for eventual elimination [74,75]. Several studies showed that decreased expression of ApoA1 was associated with neurodegenerative diseases with cognitive impairment [76]. Decreased ApoA1 in plasma and increased ApoA1 in CSF were reported after brain injury. We propose that ApoA1 is associated with CICI involving TNFalpha following treatment with Dox [3,76].

ApoA1 regulates anti-inflammatory reactions by activation JAK2 and STAT3 as a result of ApoA1 interacting with the cholesterol

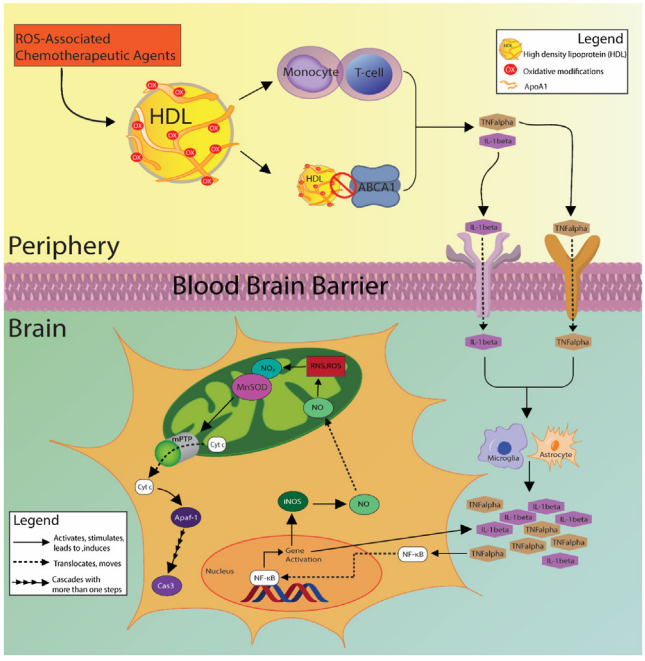

Fig. 1. Proposed mechanism of cytokine-induced CICI following ROS-associated chemotherapy.

transport protein ABCA1, decreasing release of pro-inflammatory cytokine from macrophage [76–78]. Secretion of TNFalpha and IL-1beta from stimulated T cells and monocytes also was inhibited by ApoA1 [79]. With evidence that ApoA1 is oxidized by 4-HNE in plasma after Dox treatment in humans and that oxidized ApoA1 failed to prevent LPS-induced TNFalpha release from macrophage culture [80], one can envisage a scenario of chemotherapy induced oxidation of ApoA1, which changes its structure and therefore changes its interaction with ABCA1, leads to elevation of proinflammatroy cytokine levels in plasma. These elevated cytokines in plasma translocate to brain by receptor-mediated endocytosis, leading to oxidative stress, mitochondira dysfunction, apoptotic cell death, and subsequent cognitive impairment.

The proposed mechanisms of cytokine-mediated CICI are discussed below and expressed in Fig. 1, using TNFalpha and IL-1beta as examples. Cytotoxic anti-cancer drugs, such as Dox, cause the oxidative stress in the plasma of cancer patients. Oxidized ApoA1 triggers immune response and inflammatory reactions by the possible binding between monocyte and T-cell, or dysregulation of combination of ApoA1 and ABCA1 followed with disruption of JAK2/STAT3 pathway. Inflammatory cytokines including IL-1beta and TNFalpha as the result of oxidation of ApoA1 in periphery then are transported through BBB. For example, TNFalpha recruits TNF receptor I or II (mostly TNFRI) [81,82] to cross the BBB by receptor-mediated endocytosis. Cytokines activate glia and astrocytes once they enter into CNS and amplified local cytokine production ensues. Elevated TNFalpha in brain activates NF-κB leading to increased expression of IL-1beta, induction of iNOS and further TNFalpha production. Elevated NO as a result of iNOS expression leads to nitrosative stress in brain and nitration of MnSOD, an important primary antioxidant defense in mitochondria. Damaged MnSOD fails to protect neurons from over-produced ROS and RNS, decreasing mitochondrial regular functions followed with formation of mitochondrial permeability transition pore and cytochrome C release. As a consequence of these serial reactions, apoptotic brain cell death is triggered and structures and functions of several cognition-related areas in brain are altered, leading to cognitive impairment.

1.6. Treatment and prevention of CICI

Possible adjuvant treatment along with chemotherapy could be posited based on the cytokine releasing mechanism outlined above. Inhibition of ZAK by nilotinib and sorafenib were shown to inhibit Dox-induced activation of P38 MAPK/JNK and downregulating IL-1beta in macrophage [83]. ApoA1 and its associated JAK2/STAT3 pathway could be biomarkers for diagnosis and prevention of CICI. Pharmacological upregulation of neuroprotective cytokines could be considered as an adjuvant approach to reduce or prevent the cognitive symptoms induced by chemotherapy.

Vitamin D (VitD) is shown to participate in regulation of CNS homeostasis [65,84]. Suppression of NO and inflammatory cytokines including TNFalpha and IL-6 by $1\alpha,25(OH)_2$ $VitD_3$ was shown in activated microglia [85]. These results suggest that VitD supplements in diet potentially could increase the defense in brain against CICI-related local inflammation. This approach conceivably could have relevance to those persons undergoing chemotherapy who live northern regions during the winter when sun exposure is minimized.

Mesna (2-mercaptoethane-1 sulfonate, sodium salt) is an adjuvant shown to suppress lipid peroxidation in plasma without alleviating cancer drug functions [86] as its negative charge makes Mesna unable to enter cancer cells [3]. Mensa is often prescribed for persons being treated with regimens of ifosphamide and/or cyclophosphamide chemotherapy to prevent hemorrhagic cystitis in bladder by scavenging the metabolic by-product of these drugs, acrolein [3,87]. Dox induced peripheral oxidative stress and inflammation were prevented by co-administration of Mesna that also resulted in less oxidized ApoA1 and decreased TNFalpha release [3,80]. As TNFalpha elevation is proposed to play an important role in the mechanism of CICI, Mesna conceivably could be a reasonable adjuvant to reduce side effects of Dox or even other chemotherapeutic agents: Over one half of FDA approved anti-cancer drugs generate reactive oxygen species, and ROS could cause oxidation of plasma proteins including ApoA1 [80]. However, a pilot study of approximately 30 subjects treated with Mesna or saline in the first chemotherapy session, followed by a crossover approach for the second chemotherapy period with Dox, the chemotherapy agent given, yielded only modest protection against plasma oxidative stress, and even then, only in patients who had high initial levels of TNFalpha [88]. Clearly, more clinical studies are required to determine if Mesna will provide positive effects on behavioral studies, neuropsychological testing, and brain structural and functional changes.

2. Conclusion

There is still not a completely proven mechanism of chemotherapy induced cognitive impairment due to the complications of chemotherapy and cancer itself. A number of confounding aspects in the clinical trials add to difficulties in studying mechanisms of CICI. Lack of human samples before chemotherapy is a main problem for both longitudinal and cross-sectional studies. Beside individual diversity of human beings, fatigue, anxiety and other clinical aspects can lead to psychological symptoms that could affect physiological changes and cause deviations in the data collection and further data analysis. More careful clinical trial design is required for both longitudinal and cross-sectional studies with reliable control groups and fewer confounders. Cytokine dysregulation could be considered as a main initiation or key factor in the process of chemotherapy induced cognitive impairment. Continued studies will focus on ROS generation of oxidized ApoA1, leading to a series

of biochemical steps to TNFalpha-mediated CICI. Such studies are in progress in our laboratory.

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