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EXTRA VIEW

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Chemo brain: From discerning mechanisms to lifting the brain fog—An aging connection

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ABSTRACT

Mounting evidence indicates that cancer treatments cause numerous deleterious effects, including central nervous system (CNS) toxicity. Chemotherapy-caused CNS side effects encompass changes in cognitive function, memory, and attention, to name a few. Although chemotherapy treatment-induced side effects occur in 16–75% of all patients, the mechanisms of these effects are not well understood. We have recently proposed a new epigenetic theory of chemo brain and, in a pioneer study, determined that cytotoxic chemotherapy agents induce oxidative DNA damage and affect molecular and epigenetic processes in the brain, and may be associated with brain aging processes.

In this paper, we discuss the implications of chemo brain epigenetic effects and future perspectives, as well as outline potential links with brain aging and future translational research opportunities.

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Introduction - neurotoxicity of chemotherapy

Elevated cancer rates have resulted in increased awareness and thus the outpouring of research seeking new ways to improve cancer prevention, achieve effective early detection and precise diagnostics, and, most important of all, develop effective treatment options. Ensuring that cancer patients have the best possible quality of life and suffer minimum side effects from their treatments is of utmost importance. Chemotherapy is a key cancer treatment strategy. The vast majority of cytotoxic chemotherapy agents target rapidly dividing cells, including both cancer cells and normal cells that are growing and dividing. As such, these agents can have numerous toxic side effects, such as hair loss, skin changes, gastro-intestinal syndromes, and dysfunction of the bone marrow, among many other effects.[1,2]

The brain is the key coordinating organ that is responsible for every function of our bodies. Cancer treatment side effects also manifest in central nervous system (CNS) toxicity.[3] Recent research shows that chemotherapy agents are, in fact, more toxic to healthy brain cells than to the cancer cells they were designed to treat.[4] Chemotherapeutic drugs cause side effects in the cognitive domains of memory, attention, processing speed, and executive function, and these chemotherapy-induced persistent cognitive dysfunction.[5-12] This condition, often described by patients as *brain fog*, is called "chemo brain".[13] The duration of chemo brain symptoms ranges from short to long,[14-16] with around one third of patients reporting side effects for months to as long as 5 to 10 y after the cessation of their treatments.[13,17]

In breast cancer alone, more than 60 studies have investigated and found various degrees of association between chemotherapy and cognitive impairments.[18] Nevertheless, which cognitive domains are most affected and most vulnerable to chemotherapy treatment remain unclear. This knowledge gap is due to the multifactorial nature of the neuropsychological tests used in various clinical studies.[19] In a longitudinal study by O'Farrel et al., they found the following 4 cognitive factors that were affected in cases of chemo brain: processing speed, working memory, visual memory, and verbal memory. These test findings agree well with patients' self-reports of experiencing losses in cognitive function.[19] At the same time, other studies have found that self-reported cognitive function impairment is weakly correlated with testing performance on neurocognitive tasks.[20] However, this dichotomy may suggest that tests of neurocognitive tasks may be not fully accurate in assessing how well patients perform in their everyday lives. Subjective reports of impairment from patients, while providing grounds that issues occur in post-chemotherapy treatment, are based on assignments of cognitive tests that assess a particular cognitive domain. A recent elegant scoping review by Olson and colleagues[21] focused on the comprehensive cognitive assessment of adult cancer chemotherapy patients concluded that while cognitive function is a constant and burning concern of individuals diagnosed with cancer, "additional research is needed to find an objective testing protocol that is more highly correlated with perceived cognitive changes".[21] Nevertheless, current clinical reports do not provide any information on the molecular and cellular changes that go on in the brain and serve as a foundation for cognitive deficits.

New insights into mechanisms of chemo brain

The underlying mechanisms of chemotherapy-related cognitive dysfunction need to be further elucidated.[22] Recently,

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increasing amounts of data have shown that chemotherapy imposes toxic effects on the cellular populations of the CNS.[22] Chemotherapy induces oxidative stress and apoptosis, inhibits neuronal proliferation and differentiation, activates microglia, and affects chromatin remodeling, leading to the aberrant expression of neurotrophic proteins in the brains of experimental animals.[5-11] These molecular changes are linked to altered neurogenesis and deficits in learning and memory.[12,23,24] Furthermore, the frequency and timing of chemo brain occurrence and persistence suggest that its origins may be epigenetic and associated with aberrant global gene expression patterns.[25] Epigenetic changes are defined as "meiotically heritable and mitotically stable alterations in gene expression" that "include DNA methylation, histone modification and RNA-associated silencing".[26-28] Epigenetic changes play key roles in brain and behavior.[29,30]

In a recent pioneer study in *Aging* (2016)[31] we have proposed a new theory of chemo brain in which the mechanisms that underlie the neurotoxic side effects of chemotherapy on the brain are epigenetically regulated and associated with altered gene expression.[31] Our analysis focused on the hippocampus and prefrontal cortex (PFC) and was based on their pivotal roles in memory, learning, and executive functions. The PFC is at the foremost section of the frontal lobes. It is involved in "executive functions," such as decision making, planning and judgment, and working memory. It is also regulates abstract thinking and social behavior.[32,33] The PFC undergoes prolonged development and is extensively interconnected with other cortical, subcortical, and brain stem sites.[32] The hippocampus is a part of the limbic system and is located within the medial temporal lobe. It regulates several cognitive processes, including spatial navigation and memory processing.[34] It plays major roles in the storage of long-term memory and in declarative memory, which concerns things that can be recalled with purpose, such as facts or events.[35]

We dissected the molecular mechanisms of chemo brain by using a murine model, and we analyzed epigenetic and gene expression changes in the hippocampus and PFC tissues of mice 24 hours and 3 weeks after treatment with cytotoxic chemotherapy agents mitomycin C (MMC) and cyclophosphomade (CPP), 2 agents that have been shown to cause chemo brain; however, the mechanisms of their effects remained elusive.[31] Our data showed that MMC and CPP treatments lead to drug-, sex-, and brain region-specific and persistent changes in global gene expression profiles. Overall, gene expression responses were much more profound for MCC than CPP exposure, and they were most prominent in the PFC tissues of female animals 3 weeks after MMC treatment, affecting pathways responsible for oxidative stress and other effects. Mitomycin C treatment caused oxidative stress, accumulation of 8-oxodG, decreased global DNA methylation, and increased DNA hydroxymethylation in the PFC tissues of female animals. The molecular changes caused by MMC exposure persisted for up to 3 weeks and were most pronounced in the PCF tissues of female animals. The results show that the PFCs of females may be more vulnerable than those of males in the long-term because the significant changes observed in females at 3 weeks post-exposure to MMC were not apparent in males. Moreover, the majority of the changes induced by MMC in the PFC tissues of female mice resembled those that occur during aging processes, suggesting that chemotherapy exposures may accelerate brain aging.

Reflections and future perspectives – from mechanisms to aging links

In our pioneer study,[31] we used Illumina mRNA profiling technology to determine that chemotherapy exposures cause gene expression changes in rodent brain, although mRNAs constitute only a small portion of cellular RNA makeup. Genome sequencing, as well as recent advances in non-coding RNA biology, has shown that more than 98% of our genes encode RNA molecules that are never translated into proteins.[36,37] These non-coding RNAs (ncRNAs) are structurally and functionally diverse, and many of them partake in the regulation of cellular proliferation, differentiation, apoptosis, stress responses, and control of genome stability.[38-40,41] Among the large repertoire of cellular ncRNAs, microRNAs and piwi-interacting RNAs are implicated as important players in the regulation of neuronal development and function, aging and neurodegeneration, and a variety of neurologic diseases, such as Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, stroke, Huntington's disease, and brain cancers, as reviewed in.[42-47] Chemo brain has not been explored in terms of the small ncRNA domain. Future research that examines the effects of chemotherapy on non-coding RNAs in the brain is both interesting and important.

We determined that chemotherapy exposure causes changes in global genome DNA methylation and hydroxymethylation.[48] These epigenetic phenomena are essential regulators of gene expression,[26,42 49] and are important in health and disease,[48] including cognitive regulation, memory and aging.[50-52] Our data show the overall net changes in the amount of 5 mC and 5 hmC in the genome but lack details on the genomic distribution and locus specificity of the observed changes. Alterations in DNA methylation have been shown to occur in defined regions.[53] Future studies should be conducted to determine the distribution and plasticity of DNA methylation and hydroxymethylation in a quantitative fashion and to correlate genome-wide and promoter-specific DNA methylation and hydroxymethylation patterns with the levels of gene expression.[49,54,55] This approach will help analyze the regulation of gene expression by chemotherapy exposure. In addition, looking into the role of transcription factors in the regulation of gene expression responses to chemotherapy drugs would likewise be important, especially in context of brain aging.

Our study focused on the effects of 2 cytotoxic chemotherapy agents, MMC and CPP, on the brain. Notably, CNS side effects have been reported to occur upon exposure to 'targeted' chemotherapy drugs, such as proteasome inhibitors (bortezomib), topoisomerase inhibitors, bevacizumab, trastuzumab, and small-molecule tyrosine kinase inhibitors (TKIs), to name a few.[3] Among these, bevacizumab is a recombinant monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A. Trastuzumab (i.e., Herceptin) is a monoclonal antibody that interacts with HER2. Gefitinib is one of many oral small-molecule TKIs that block the ErbB-1 receptor.[56] The molecular targets of many of these agents are

involved in cancer, but they may also be important for brain function. Little is known about the effects of targeted drugs on the brain or on the mechanisms of chemo brain induction by these new targeted chemotherapy agents, as well as any potential pro-aging effects of targeted chemotherapy. While new techniques are being developed to better tailor individual drugs to individual patients with the use of new platforms, such as the OncoFinder algorithm,[57-59] conducting individualized predictions of any possible side effects, especially severe ones that involve the CNS, will also be important. Recent modifications to the OncoFinder algorithm allow the personalized screening of nootropic drugs,[60] as well as the analysis of the effects of small RNA (MiRImpact) on signaling pathways.[61] With thorough animal studies, OncoFinder and MiRImpact may be further developed and enabled to predict possible targeted chemotherapy-induced brain side effects.

Given that chemotherapy exposure leads to molecular epigenetic changes, analyzing neuroanatomical and behavioral post-chemotherapy outcomes is an interesting area for future study. Moreover, our studies and the available data on chemo brain used healthy animal models that, while treated with chemotherapy drugs, lacked one important component—the presence of an actual tumor. Investigating chemo brain in tumor-bearing animals is essential to gain a full understanding of the molecular mechanisms and pathways affected in chemo brain. Chemo brain is hypothesized to manifest itself in tumor-bearing mice and is more pronounced in treated animals than in untreated ones, whereas the presence of a tumor itself also affects molecular networks in the brain.

On another note, the phenomenon of chemo brain has not been fully explored in the aging domain. Chemotherapy may cause changes that lead to neuroinflammation and brain aging.[21,62] As highlighted at the recent conference on biomedical innovations for healthy longevity, the mechanism and role of cancer treatment-caused aging-related changes need to be analyzed because it will allow the development of strategies for the prevention and mitigation of treatment-induced neurodegeneration and aging.[63] To that effect, a new computational tool, the GeroScope, may be used to determine pro-aging and anti-aging pathways altered by chemotherapy exposures in the brain.[64]

Even more crucial would be the study of chemo-treatment side effects in adolescents and children. For children in developed countries, cancer is the second most common cause of death after accidents. In Canada, 10,000 children live with cancer today, and 1,500 new cases are diagnosed each year. Among these, leukemia is the most common pediatric cancer, accounting for 30% of all malignancies diagnosed annually in children aged younger than 15 (http://childhoodcancer.ca/education/facts_figures). In 1960, the survival rate of pediatric leukemia patients was very low at about 10%. Nowadays, 80–85% of leukemia patients survive, but many of them suffer debilitating side effects, including severe manifestations of chemo brain, leading to huge losses in productive years of life.[65-67] In the future, animal model studies can help shed light on the molecular mechanisms and behavioral repercussions of pediatric chemo brain effects.

One other poorly studied aspect of chemo brain is the possibility of treatments that might reverse, or at least reduce, its manifestations. Such treatments could be based upon strategies devised for rehabilitation after brain injuries in animal models, such as complex housing, exercise, tactile stimulation, and psychomotor stimulants, among others. Moreover, given a link between chemo brain and aging, some of the novel geroprotectors can be explored in the anti-chemo brain domain.[68]

Preclinical animal model data can serve as a foundation for the research and development of new chemo brain biomarkers. Our studies can be used as a roadmap for the development of tests that will predict sensitivity to radiation and chemo brain side effects. Molecular changes observed in the brain must first be correlated with those observed in blood to find effective biomarkers. The markers (small RNAs or mRNAs) that will be correlated between blood and the brain in animal models may be further explored to determine their usefulness in human studies. Last but not the least, animal models may be used to develop future strategies and interventions that help prevent and mitigate chemo brain.

Disclosure of potential conflicts of interest

No potential conflicts of interest were received.

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