The Triangle of Death of Neurons in Chemotherapy Induced Cognitive Impairment ("Chemobrain")

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Abstracts will be considered for both poster and platform presentations

Cognitive/Behavioral disorders

The Triangle of Death of Neurons in Chemotherapy Induced Cognitive Impairment ("Chemobrain"): Oxidative Damage, Mitochondrial Dysfunction, and Loss of Choline-Containing Biomolecules in Brains of Mice Treated with Doxorubicin Provide Advanced Insights into Mechanisms

Depending on the published study, from 30 % to 70 % of cancer survivors who had undergone chemotherapy reported cognitive dysfunction, usually manifested as memory impairment, difficulty with reasoning, and problems multi-tasking, consistent with deficits of higher executive functioning. This chemotherapy induced cognitive impairment (CICI), often called "chemobrain" by patients, is a major contributor to decreased quality of life for a large percentage of the more than the current 15 million cancer survivors in the USA.
More than 50 % of FDA-approved anti-cancer drugs are associated with reactive oxygen species (ROS) as part of their mechanisms of action. Doxorubicin (Dox) is a prototypical ROS generating chemotherapeutic agent used to treat solid tumors and lymphomas as part of multi-drug chemotherapeutic regimens. Dox produces the reactive superoxide radical anion (O2-•) in vivo through quinone to semi-quinone redox cycling. Neither Dox nor its major metabolite cross the blood brain barrier.
We previously reported that intraperitoneal (i.p.) Dox-administration to mice leads to plasma protein damage and elevation of tumor necrosis factor-alpha (TNF-α) in plasma and brain. We further reported that TNF-α elevation in brain leads to further central nervous system toxicity including oxidative stress, mitochondrial dysfunction, neuronal death, and cognitive impairment. In the present study, we tested the hypothesis that TNF-α in brain was critical to these deleterious effects that contribute to CICI. We demonstrate that oxidative stress is ameliorated and mitochondrial function assessed by the Seahorse-determined oxygen consumption rate (OCR) is preserved in brain of Dox-treated TNF-α knockout (TNFKO) mice. Further, we show in TNFKO mouse brain protection against Dox-related decreased Cho/Cr ratio determined by magnetic resonance spectroscopy (MRS) and protection against loss of phospholipase D (PLD) activity. Coupled with findings from our previous studies, these current results provide important insights into the role of TNF-α in CICI and identify potential therapeutic targets to prevent this debilitating condition and improve the quality of life of cancer survivors.

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