Study sheds light on fatty acid's role in 'chemobrain' and multiple sclerosis

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Medical experts have always known myelin, the protective coating of nerve cells, to be metabolically inert. A study led by The University of Texas MD Anderson Cancer Center has found that myelin is surprisingly dynamic, a discovery that has implications for treatment of multiple sclerosis and a type of myelin damage caused by some chemotherapy drugs, often referred to as "chemobrain." Chemobrain can occur in up to 70 percent of patients receiving chemotherapy, leaving them with temporary and even permanent thinking and memory impairment.

Study findings were published in the March 23 online issue of the *Journal of Clinical Investigation*.

Myelin is comprised of fatty substances and proteins, and when wrapped around neural nerves such those found in the brain and spinal cord, allows electrical impulses to transmit quickly and efficiently along the nerve cells. Diseases such as multiple sclerosis occur when myelin is damaged, a process known as demyelination.

"We actually found that mature myelin is often damaged when cancer patients are treated with various types of chemotherapy drugs and is probably the most consistent manifestation of chemotherapy-induced neurotoxicity," said Study Lead, Jian Hu, Ph.D., assistant professor of Cancer Biology. "Our study shows that mature myelin is a very dynamic material, particularly its lipid components, and it disproves a dogma held for decades, if not a century, that mature myelin is a very stable substance."

Hu's team shows that mature myelin lipids undergo rapid turnover and require an RNA-binding protein known as the quaking or Qki to perform normally. Qki depletion resulted in quick demyelination and gradual neurologic deficits when observed in mice.

Significantly, Qki served as a co-activator of the neural signaling proteins called peroxisome proliferator-activated receptors (PPAR), which play a role in controlling transcription of lipid metabolism genes by working with their partners retinoid X receptors (RXRs). Hu's team found that Qki interacts with a PPAR isoform called PPAR-beta and RXR-alpha to modulate this transcription, opening up a potential new approach to treating demyelination.

"Treatment of Qki-depleted mice with drugs like PPAR-beta or RXR-alpha agonists greatly alleviated neurological disability and extended survival durations," said Hu. "Furthermore, a subset of lesions from patient samples with primary progressive multiple sclerosis were characterized by downregulation of key activities in lipid metabolism associated with Qki and PPAR-beta/RXR-alpha."

"Together, the team demonstrated that continuous lipid production is indispensable for mature myelin maintenance and highlights an underappreciated role of lipid metabolism in demyelinating diseases and cancer therapy related adverse effects such as chemobrain", Hu said.

Provided by University of Texas M. D. Anderson Cancer Center

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