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Researchers see possible answer to chemo pain in a multiple sclerosis drug

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In a recently published study in the *Journal of Biological Chemistry*, Saint Louis University professor of pharmacological and physiological sciences Daniela Salvemini, Ph.D. describes two discoveries: a molecular pathway by which a painful chemotherapy side effect happens and a drug that may be able to stop it.

"The chemotherapy drug paclitaxel is widely used to treat many forms of cancer, including breast, ovarian and lung cancers," said Salvemini. "Though it is highly effective, the medication, like many other chemotherapy drugs, frequently is accompanied by a debilitating side effect called chemotherapy induced peripheral neuropathy, or CIPN."

CIPN can appear as tingling or numbness in the hands and feet, shooting or burning pain in the limbs, or can feel like hot or cold temperature extremes. Symptoms may resolve within weeks or months of stopping the chemotherapy treatment or may last for years. In addition to causing patients suffering, CIPN is often a limiting factor when it comes to treatment.

Physicians estimate that CIPN can occur in 30 to 90 percent of patients treated with taxanes (the class of drugs that includes paclitaxel) and combination chemotherapies.

Salvemini and her colleagues studied paclitaxel, which also is known as Taxol, and discovered that the pain pathway (the series of interactions between molecular-level components) is dependent on activation of

sphingosine 1-phosphate receptor subtype 1 (S1PR1) in the central nervous system by engaging a series of damaging neuro-inflammatory processes leading to pain. By inhibiting this molecule, they found that they could block and reverse paclitaxel-induced neuropathic pain without interfering with the drug's anticancer effects.

This finding is particularly encouraging because a drug that modulates S1PR1 is already on the market. A medication called FTY720 (Gilenya) is FDA-approved as a therapy for multiple sclerosis. When Salvemini tested this drug in her lab, she found that the S1PR1 modulator weakened the neuroinflammatory processes, which in turn blocked and reversed neuropathic pain without altering the anticancer properties of paclitaxel. Further, the beneficial effects of FTY720 were not restricted to paclitaxel but also extended to another chemotherapeutic agent, the platinum based drug oxaliplatin which is widely used for metastatic colon cancer and other gastrointestinal cancers.

While clinical trials will be necessary to determine the safety and efficacy of the drug in treating CIPN, researchers are hopeful that they may be able not only to relieve cancer patients of debilitating pain, but also save more lives by permitting the administration of larger, potentially more effective doses of chemotherapy drugs.

"We have identified a critical pathway by which CIPN develops and continues that can be targeted with a drug that is already FDA approved. This does not happen often," said Salvemini. "We need to capitalize on these findings and explore use of these agents in cancer pain patients to improve quality of life and potentially maximize anticancer efficacy as soon as possible."

This study was funded by the Leukemia and Lymphoma Society Translational Research Program and the Mayday Fund with additional support from the Saint Louis University Cancer Center.

Established in 1836, Saint Louis University School of Medicine has the distinction of awarding the first medical degree west of the Mississippi River. The school educates physicians and biomedical scientists, conducts medical research, and provides health care on a local, national and international level. Research at the school seeks new cures and treatments in five key areas: cancer, liver disease, heart/lung disease, aging and brain disease, and infectious disease.

More information: *Journal of Biological Chemistry*, www.jbc.org/content/early/2014 … M114.569574.abstract

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