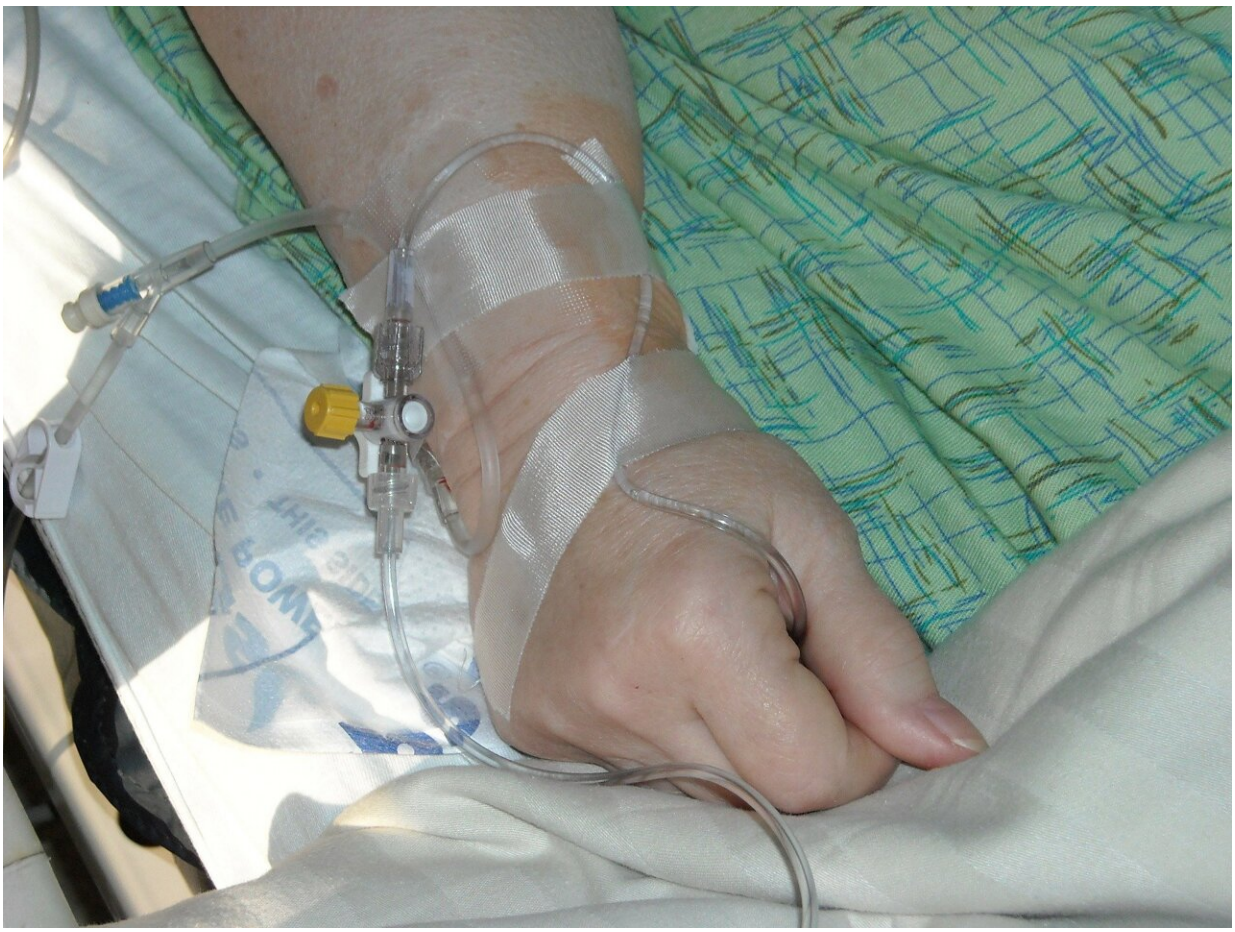
Researchers identify mechanism involved in development and intensification of cancer treatment-related pain

January 30 2023, by Luciana Constantino



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A combination of chemotherapy and drugs that stimulate the immune system to combat cancer is increasingly used to control progression of the disease in patients. On the other hand, clinical studies show that the combination has adverse side effects, such as peripheral neuropathy characterized by pain, numbness, tingling, sensitivity to cold in the hands and feet, and sometimes in the arms and legs. These problems can lead to suspension of the treatment.

A group of Brazilian researchers set out to follow up on these clinical observations by investigating the mechanisms that trigger side effects of two drugs used in combination to combat lung and breast cancer —paclitaxel and immune checkpoint inhibitors anti-PD1 and anti-PDL1.

Paclitaxel is a chemotherapy drug widely distributed by the SUS (Sistema Unificado de Saúde), Brazil's national health system, for several types of cancer. In many patients, it causes adverse side effects such as peripheral neuropathy. Immune checkpoint inhibitor therapy is relatively new and has revolutionized the treatment of certain types of advanced cancer by promoting anti-tumor immune responses.

However, dose-limiting side effects have been seen to increase in patients to whom these medications are administered concomitantly. The researchers sought to understand the processes involved in these adverse reactions and discovered a mechanism underlying both the development of severe neuropathic pain and the exacerbated side effects associated with the combination of the two treatments.

The study was conducted at the Center for Research on Inflammatory Diseases (CRID), a Research, Innovation and Dissemination Center (RIDC) hosted by the University of São Paulo's Ribeirão Preto Medical School (FMRP-USP).

Scientists affiliated with the São Paulo State Cancer Institute (ICESP)

and Albert Einstein Jewish Hospital (HIAE) also participated.

An article on the study is published in the journal *Cancer Immunology Research*. The findings could serve as a basis for further research on ways of combating pain associated with other diseases.

According to the article, the immune checkpoint inhibitors block interaction between PDL1 proteins present in macrophages (innate immune system cells) and PD1 receptors found in neurons. This interaction normally inhibits the neuropathic pain caused by the damage done by paclitaxel to the central and peripheral nervous systems. The inhibitors, therefore, end up intensifying this side effect.

The interaction between macrophages and neurons via PDL1 and PD1 as a pain control mechanism was not clear from previous research. "The role of this PD1-PDL1 synergy in pain control has never been so evident. Our discovery that this neuroimmune interaction can attenuate the neuropathic pain associated with cancer treatment serves as a basis for exploring the mechanism in other disease models," said Carlos Wagner Wanderley, a researcher at CRID and first author of the article, alongside Alexandre Maganin.

"Clinical trials had already found that immunotherapy combined with paclitaxel increased patient pain, suggesting neurotoxicity. This study linked basic research and clinical analysis in pursuit of a deeper understanding of the mechanism involved. The results proved significant," said Thiago Mattar Cunha, a professor at FMRP-USP and last author of the article alongside Fernando de Queiroz Cunha, professor of pharmacology at FMRP-USP and CRID's principal investigator.

"By understanding the mechanisms involved in the intensification of pain due to the combination of the two treatments, we can develop

therapeutic alternatives that prevent pain and maintain anti-neoplastic effects," Queiroz Cunha said.

A previous study, in which Mattar Cunha also took part, revealed another of the mechanisms behind the side effects caused by paclitaxel in cancer patients. The results showed that the drug binds to and activates C5aR1, a cellular receptor involved in inflammatory diseases and tumors. This connection is crucial to the origin of adverse reactions to the chemotherapy drug.

Stages of the study

The researchers gave mice paclitaxel and measured the animals' temperature, paw pressure and strength, analyzing inflammatory markers to confirm that they were experiencing neuropathic pain. In focusing on the role of PDL1 and PD1 in modulating the pain induced by the drug, they found the protein and receptor to be expressed in neural tissue. However, during the development of the adverse reactions triggered by paclitaxel, expression of PDL1 increased in peripheral nervous tissue macrophages, specifically in the dorsal root ganglion.

The researchers also observed that exogenous administration of PDL1 inhibited the pain triggered by the drug as well as other painful stimuli in the mice, suggesting that the PDL1/PD1 signaling pathway attenuated peripheral neuropathy. In addition, they found that administration of anti-PDL1 combined with paclitaxel intensified chronic neuropathy in the mice, as it often does in patients.

"The immediate impact of our research is that clinics that administer this combination of drugs can now identify patients with pain and take steps to avoid the problem, such as substituting paclitaxel," Maganin said.

More information: Carlos Wagner S. Wanderley et al, PD-1/PD-L1

Inhibition Enhances Chemotherapy-Induced Neuropathic Pain by Suppressing Neuroimmune Antinociceptive Signaling, *Cancer Immunology Research* (2022). DOI: 10.1158/2326-6066.CIR-22-0003