

ACHIEVEMENTS

Uncovering a Novel Neuro-Immune Mechanism in Lung Cancer and Paving the Way for Nerve-Targeted Cancer Therapy

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The research team presenting another breakthrough discovery in the research of treating lung cancer.

Lung cancer remains the leading cause of cancer-related deaths worldwide, with lung adenocarcinoma being the most common subtype. Immunotherapy has brought new hope to cancer patients in recent years; however, only a minor proportion of lung cancer patients have benefited from these treatments. Boosting the effectiveness of immunotherapy remains a major challenge in cancer research.

The Lung Cancer Team at National Taiwan University Hospital (NTUH) has joined forces with an international team led by Dr. Leanne Li, Group Leader at the Francis Crick Institute, to analyze a previously unknown mechanism by which lung cancer exploits the nervous system to weaken the body's immune defenses. This study was recently published in *Cell*.

The study found that lung adenocarcinoma recruits nociceptive sensory neurons—specialized sensory nerves responsible for detecting pain and harmful stimuli.



Prof. Chen remarking, "Future cancer treatment should focus not only on 'cutting off the water supply' by targeting blood vessels that nourish tumors, but on 'cutting off the electricity supply' by blocking nerve signals that promote cancer growth. Simultaneously targeting blood vessels, nerves, and the immune system may lead to more effective cancer treatment strategies."

Once activated, these neurons release signaling molecules that disrupt lung cancer immunity. This study examined the hitherto under-explored role of nerve signals in lung cancer immune evasion.

Further investigation revealed that these released nerve signals prevent the formation of key immune defense hubs around tumors. These defensive structures serve as gathering points where immune cells assemble and coordinate attacks against cancer cells, and thus are essential for controlling tumor growth.

To illustrate this concept, while normal lymph nodes can be thought of as police stations within a city, these newly formed immune hubs around tumors resemble neighborhood patrol teams that monitor suspicious activity, call for support, and help to maintain public safety. The study found that nerves surrounding lung tumors act like a communication system that continuously sends misleading signals, disrupting the formation and operation of these patrol teams. Consequently, immune cells fail to gather effectively, opening the way for uncontrolled cancer growth.

The team further validated their findings using mouse models of lung cancer. Again, blocking these nerve signals significantly enhanced the immune system's ability to attack lung cancer cells and suppress tumor growth. Besides causing genetic mutations, cigarette smoke extracts activate nociceptive neurons which further weaken the body's defenses against cancer cells. These findings suggest that, in addition to its known mutagenic role, smoking can also promote lung cancer development through a neuro-immune mechanism.

Prof. Jin-Shing Chen, Chair of the Department of Surgery at NTUH, explains: "Our study shows that cigarette smoke does more than just damage the DNA of cells. It also directly stimulates nociceptive neurons, which in turn interfere with the immune system's ability to establish effective anti-cancer defenses, making it easier for cancer cells to grow and progress. This research reveals a completely new mechanism underlying lung adenocarcinoma development."

Importantly, the study also disclosed that certain medications already approved for migraine treatment may be combined with cancer immunotherapy to further improve treatment outcomes. Animal studies have demonstrated that this combination strategy not only strengthens anti-tumor immune responses but also prolongs survival, offering a promising new avenue for lung cancer therapy.

Dr. Leanne Li affirms, "This study identified molecular mechanisms underlying the interactions among the nervous system, the immune system, and lung cancer. Our findings reveal that nerve signals are not merely messengers of pain but active participants in lung cancer progression, and could be harnessed to improve immunotherapy response. These discoveries expand the frontier of Cancer Neuroscience and provide new therapeutic targets and directions for lung cancer treatment."

Looking ahead, NTUH will continue to promote innovation in healthcare and precision medicine, accelerating the translation of groundbreaking research into clinical practice to bring new hope to patients with lung cancer worldwide.



Dr. Leanne Li, the group Leader at the Francis Crick Institute and also the senior author of the study.



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