Scientists Discover Ferroptosis Enhances Immunotherapy Efficacy in Head and Neck Cancer

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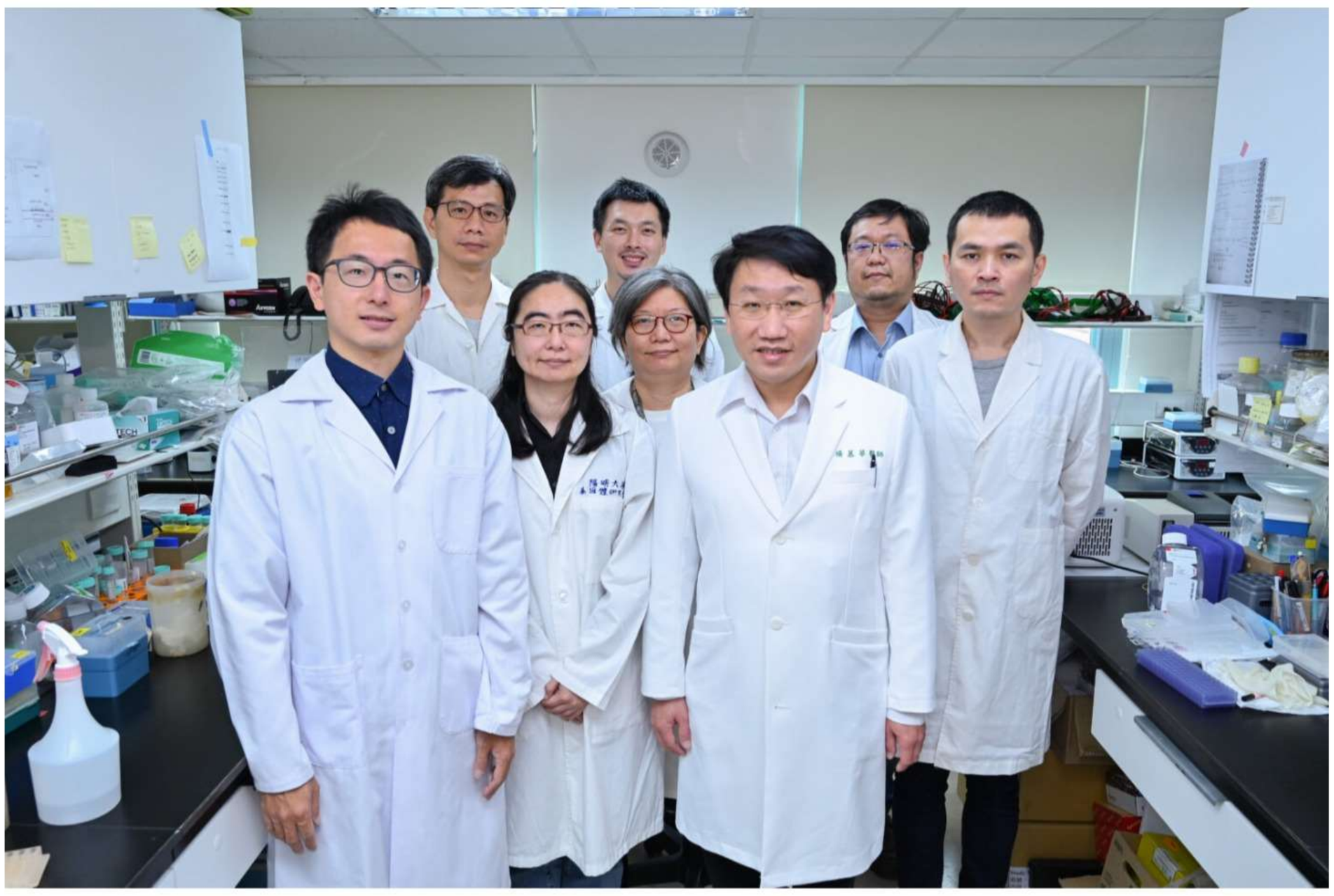
National Yang Ming Chiao Tung University (NYCU) recently made a breakthrough in head and neck squamous cell carcinoma (HNSCC) research. The research team led by Professor Muh-Hwa Yang of the Institute of Clinical Medicine, NYCU discovered that inducing iron-dependent cell death (ferroptosis) in HNSCC enhances the efficacy of cancer immunotherapy. This crucial finding was published in the international journal *Advanced Science* in April this year.



The immunoregulatory molecule PD-L1 on the surface of tumor cells serves as a critical target for immunotherapy. However, in some cases of metastatic/recurrent head and neck cancer, the expression of PD-L1 in cancer cells may be insufficient, thereby affecting the efficacy of cancer immunotherapy. The NYCU and Taipei Veterans General Hospital (VGHTPE) research team discovered that by augmenting ferroptosis signature in tumor cells, the PD-L1 expressions in tumor cells can be increased, thereby enhancing the efficacy of immunotherapy. This finding provides new insights and directions for head and neck cancer treatment strategies.

Ferroptosis, is a cell death process newly discovered in recent years. Cells generate reactive oxygen species that accumulate on the cell membrane during iron metabolism. When these reactive oxygen species cannot be cleared normally, cell death can occur.

The NYCU–VGHTPE research team analyzed HNSCC specimens and found that the ferroptosis signals in the specimens were closely related to inflammation/immune-related signatures, indicating that ferroptosis is a form of cell death that triggers an immune response. Upon further injecting ferroptosis inducers into cell lines and tumor sites in mice, the researchers observed the effect of suppression of cancer development and immune activation in the tumor microenvironment. Moreover, inducing ferroptosis in cancer cells significantly increased PD-L1 expression; thus, the combined use of ferroptosis inducers and immunotherapy demonstrated synergistic therapeutic effects in the animal experiments.

Recently, a US research team discovered that immunotherapy could increase ferroptosis in tumor cells, confirming the potential synergy of ferroptosis inducers and immunotherapy in cancer treatment. This study by NYCU directly confirms that ferroptosis itself can inhibit tumor cell growth and synergistic effects of immunotherapy can be achieved through modulation of the tumor microenvironment.

Professor Muh-Hwa Yang said that immunotherapy has clinically become mainstream in tumor treatment. Current research focuses on enhancing the efficacy of immunotherapy and improving immunotherapy response in therapy-resistant cancer cells. The present research showed that inducing ferroptosis in cancer cells to enhance immunotherapy efficacy could potentially become a new cancer treatment strategy. Although, currently, no clinically ferroptosis inducers are available, this research has revealed the ferroptosis and immunoregulation mechanisms in HNSCC treatment, which will aid in developing new treatment strategies and laying the foundation for future drug research.

This study was jointly conducted by Prof. Muh-Hwa Yang and Dr. Chih-Hung Chung's team from the Institute of Clinical Medicine at NYCU, in collaboration with Dr. Pen-Yuan Chu, Director of the Otolaryngology-Head and Neck Surgery Department at VGHTPE and Dr. Shyh-Kuan Tai, Chief of the Otolaryngology-Head and Neck Surgery Department at VGHTPE. The Cancer Progression Research Center, NYCU performed various experiments, including the spatial association of the transcriptomic signatures in the clinical specimen analysis for the study, and Assistant Prof. Chun-Yu Lin from the Department of Biological Science & Technology, NYCU, performed the advanced bioinformatics analysis.