The TVGH–NYCU Team Confirms the Oncogenicity of Circular RNA by Applying Gene-editing Technology, a Discovery with Great Potential in the Development of a New Lung Cancer Treatment

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Targeted drugs are the hope for treating cancer; but like all drugs, drug resistance is inevitable. The Taipei Veterans General Hospital–National Yang Ming Chiao Tung University (TVGH–NYCU) team has successfully applied in vivo gene-editing technology to remove a segment of the oncogenic circular RNA (circRNA) gene, confirming that the technique can inhibit the growth of cancer cells and potentially treat cancer.

Non-small cell lung cancer accounts for the majority of lung cancer cases. In Taiwan, lung adenocarcinoma is the prevailing lung cancer. Scientists have found that the activation of epidermal growth factor receptor (EGFR) on tumor cells initiates a series of signaling transduction chains in the cells, causing tumor cells to grow and metastasize. This discovery has led to the emergence of targeted drugs, which inhibit the activity of EGFR through tyrosine kinase and block the signaling transduction pathways responsible for cancer cell growth.

A research team comprising Afeez Adekunle Ishola (a Nigerian Ph.D. student in Taiwan), Dr. Shih-Hwa Chiou (NYCU Institute of Pharmacology Chair Professor), Dr. Mong-Lien Wang (TVGH Department of Medical Research Assistant Research Fellow), and Dr. Yuh-Min Chen (TVGH Department of Chest Medicine Chief) discovered that circular RNA 190 (circRNA C190) transmitted receptor signals on the cell surface to the DNA in the nucleus through the intracellular molecular pathway ERK/MAPK. Accordingly, C190 plays a crucial role in triggering the division and growth of cancer cells; can be detected in serum; reflects the current state of cancer cells. The discovery enables C190 to be used as a marker for the non-invasive diagnosis of non-small cell lung cancer in clinical settings.

Subsequently, the research team used CRISPR/Cas13a RNA editing technology to reduce the expression of C190 and found that it reduced the differentiation and migration of cancer cells, and even inhibited their growth, either in vivo or in vitro. The discovery reconfirms the role of the C190 gene in lung cancer and shows that gene therapy combined with RNA editing technology can be used as an innovative cancer treatment worthy of further development.

Professor Shih-Hwa Chiou, the principal investigator of this study, noted that circRNA is a type of RNA that was deemed as a by-product of RNA transcription with no main function, a view that has been overturned by recent research. Professor Chiou stated that the TVGH–NYCU team has detected, in their past research, more C190 manifestations in the blood of patients with terminal lung cancer; the presence of C190 implies poor treatment outcomes. C190 is closely related to tumor size, depth of invasion, metabolism, and survival rate.

This study unprecedentedly combined gene therapy with RNA editing technology to eliminate oncogenic circRNA C190. Unlike targeted drugs that block EGFR, RNA editing can directly target key genes to block cancer cell signaling.

This study was published in *Cancer Research* in February of 2022. The first author, Afeez Adekunle Ishola, a student in the Taiwan International Graduate Program organized by Academia Sinica, obtained a Ph.D. in Molecular Medicine from NYCU and Academia Sinica earlier this year. This shows that the TVGH–NYCU team highly values international research talent. The research team has received support from the Ministry of Science and Technology and the Ministry of Education through the Higher Education Sprout Project and has worked with National Institutes of Health and other agencies in the United States to achieve multinational research cooperation, thereby increasing the international visibility of Taiwan's research results.