Scientists use exosomes secreted by living cells to successfully target TKI-resistant cancer

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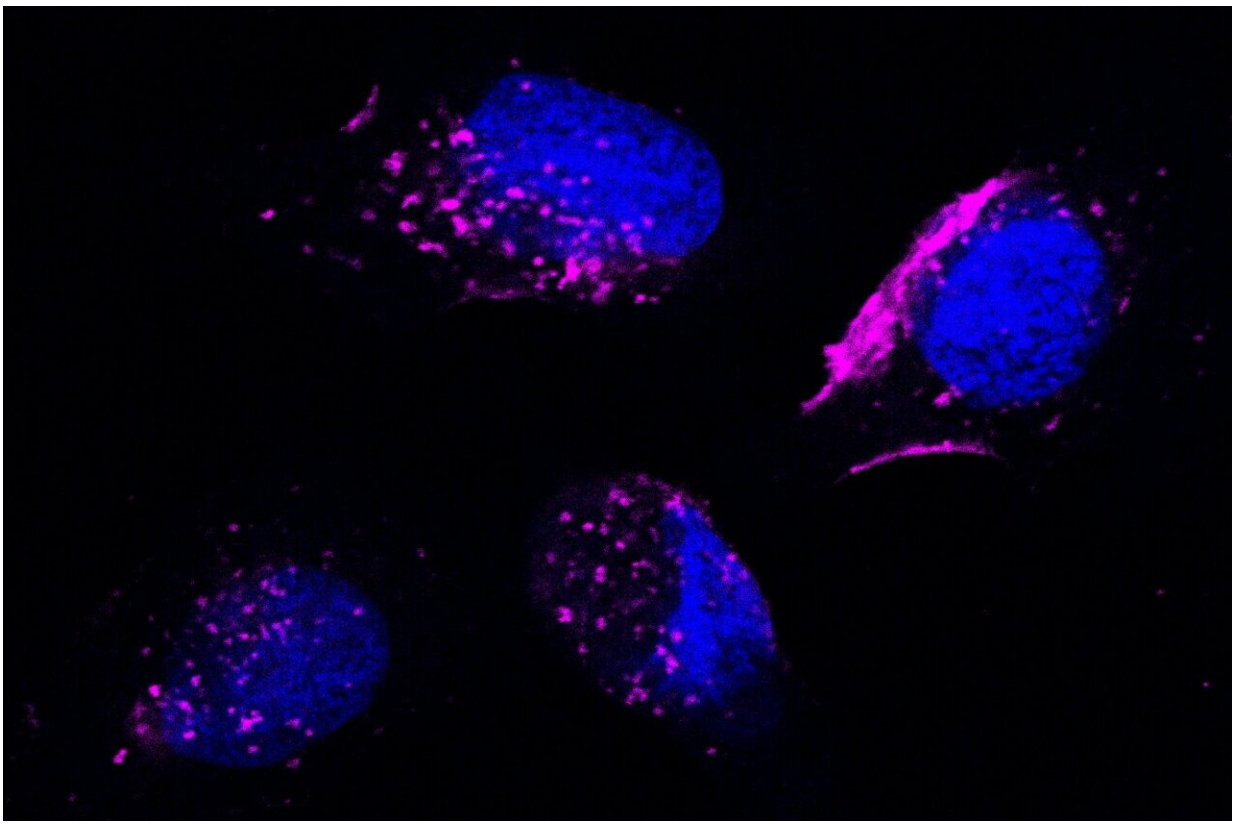

An image of head and neck cancer cells (in blue) treated with exosomes (in magenta). Credit: National Cancer Center Singapore

In a new study, clinician-scientists and researchers from the National

Cancer Center Singapore (NCCS) have demonstrated the use of exosomes to successfully target squamous cell cancer tumors that are usually resistant to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs).

Their research is the first where exosomes have been applied to target TKI-resistant cancers in Singapore. The findings were published in the journal *Developmental Cell*.

Epidermal growth factor receptor, also known as EGFR, is a biomarker frequently implicated in cancer and EGFR-TKIs are a class of drugs commonly used to target EGFR and treat the disease. However, the success of these cancer therapeutics has been variable, and many tumors with high levels of EGFR are resistant to TKIs.

The discovery

One of the biggest groups of EGFR-implicated cancers are squamous cell cancers, one of the deadliest cancers worldwide. Professor Gopal Iyer, Head of the Department of Head and Neck Surgery, Division of Surgery and Surgical Oncology, Singapore General Hospital and NCCS, treats head and neck squamous cell cancers (HNSCC) in which over 80–90% of tumors have overexpressed EGFR.

While treating patients in the clinic at NCCS, he observed that the majority do not respond to drugs targeting EGFR.

In 2017, Prof Iyer and his research team identified mutations in a rare subset of HNSCC patients that conferred sensitivity to EGFR-TKIs. The mutation resulted in a number of changes: low expression of EGFR-AS1 and high expression of EGFR isoform D. Only 3–5% of HNSCC harbor these mutations, leaving the rest of the patient group without an effective treatment.

Using exosomes in cancer treatment

Since the initial discovery in 2017, Prof Iyer and team have worked on extending their initial findings for application to a larger group of patients.

In their most recent work, they found that the EGFR isoform D produced by sensitive tumors had certain characteristics that allowed it to be secreted. Using patient-derived HSNCC cell lines in the lab, they were able to show that EGFR isoform is carried as a cargo in exosomes, and these were taken up by adjacent cancer cells and made them sensitive to TKIs.

Exosomes, which are excreted by all living cells, contain cell parts such as DNA, RNA, lipids, and proteins. They are secreted into circulation and affect the function and behavior of other cells they encounter. This communication has been shown to influence the development of various diseases, including inflammatory diseases, neurodegenerative diseases and cancer, which has made using exosomes a new and promising field for medical treatments.

The team then tested whether this characteristic of sensitivity conferred by high levels of the EGFR isoform D, was transferrable from a sensitive cancer to a resistant cancer. They produced large volumes of exosomes producing EGFR isoform D in the lab and treated a number of cell lines that were resistant to TKIs.

The exosomal treatment was able to increase the sensitivity of the resistant cell lines to many different types of TKIs. Remarkably, they were able to achieve the same result in vivo using a mouse model, confirming that it is possible to target EGFR TKI-resistant tumors with this strategy.

Opening a treasure chest

Professor Iyer, who is also Head of the translational research Division of Medical Sciences at NCCS said, "Our findings provide new hope for patients as we can potentially target a large population who previously had poor prognosis for their cancer. We're excited to partner industry to move this research to the next phase so that we can start offering therapeutic solutions to our patients in the clinic."

"We have opened a treasure chest of how exosomes can potentially be applied to transfer treatment-sensitivity for other cancers. The possibilities are endless for the future of exosomes as yet another weapon in the fight against cancer."

The research team plans to scale up exosome production so that the findings can be taken into early-stage clinical trials. They are currently in discussions with various industry and academic partners to achieve this goal.

More information: Shen Yon Toh et al, Therapeutic application of extracellular vesicular EGFR isoform D as a co-drug to target squamous cell cancers with tyrosine kinase inhibitors, *Developmental Cell* (2024). DOI: 10.1016/j.devcel.2024.07.003

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