New genes and natural toxins offer hope for cancer patients unresponsive to chemotherapy

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Scientists from Queen Mary University of London have discovered two new genes that cause head and neck cancer patients to be resistant to chemotherapy, and that silencing either gene can make cancer cells previously unresponsive to chemotherapy subsequently respond to it.

The two genes discovered actively 'work' in most human cancer types, meaning the findings could potentially extend to other cancers with elevated levels of the genes.

The researchers also looked through a chemical library, commonly used for drug discovery, and found two substances that could target the two genes specifically and make resistant cancer cells almost 30 times more sensitive to a common chemotherapy drug called cisplatin.

They do this by reducing the levels of the two genes and could be given alongside existing chemotherapy treatment such as cisplatin. One of these substances is a fungal toxin—Sirodesmin A—and the other—Carfilzomib—comes from a bacterium. This shows that there may be existing drugs that can be repurposed to target new causes of disease, which can be cheaper than having to develop and produce new ones.

The research, led by Queen Mary and published in *Molecular Cancer*, is the first evidence for the genes NEK2 and INHBA causing chemoresistance in head and neck squamous cell carcinoma (HNSCC) and gene silencing of either gene overturning chemoresistance to multiple drugs.

The scientists first used a method known as data mining to identify genes that may be affecting tumor responsiveness to drug therapy. They tested 28 genes on 12 strains of chemoresistant cancer cell lines, finding four 'significant' genes that were particularly responsive that they then investigated further and tested multi-drug resistance.

Dr. Muy-Teck Teh, senior author of the study from Queen Mary University of London, said, "These results are a promising step towards cancer patients in the future receiving personalized treatment based on their genes and tumor type that give them a better survival rate and treatment outcome.

"Unfortunately, there are lots of people out there who do not respond to chemotherapy or radiation. But our study has shown that in head and neck cancers at least it is these two particular genes that could be behind this, which can then be targeted to fight against chemoresistance.

"Treatment that doesn't work is damaging both for the NHS and patients themselves. There can be costs associated with prolonged treatment and hospital stays, and it's naturally extremely difficult for people with cancer when their treatment doesn't have the results they are hoping for."

90% of all head and neck cancers are caused by HNSCCs, with tobacco and alcohol use being key associations. There are 12,422 new cases of head and neck cancer each year, and the overall five-year survival rate of patients with advanced HNSCC is less than 25%. A major cause of poor survival rates of HNSCC is because of treatment failure that stems from resistance to chemotherapy and/or radiotherapy.

Unlike lung and breast cancer patients, all HNSCC patients are treated with almost the same combinations of treatment irrespective of the genetic makeup of their cancer.

Provided by Queen Mary, University of London

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