Medical Xpress

'Genetic rewiring' drives cancer's drug resistance

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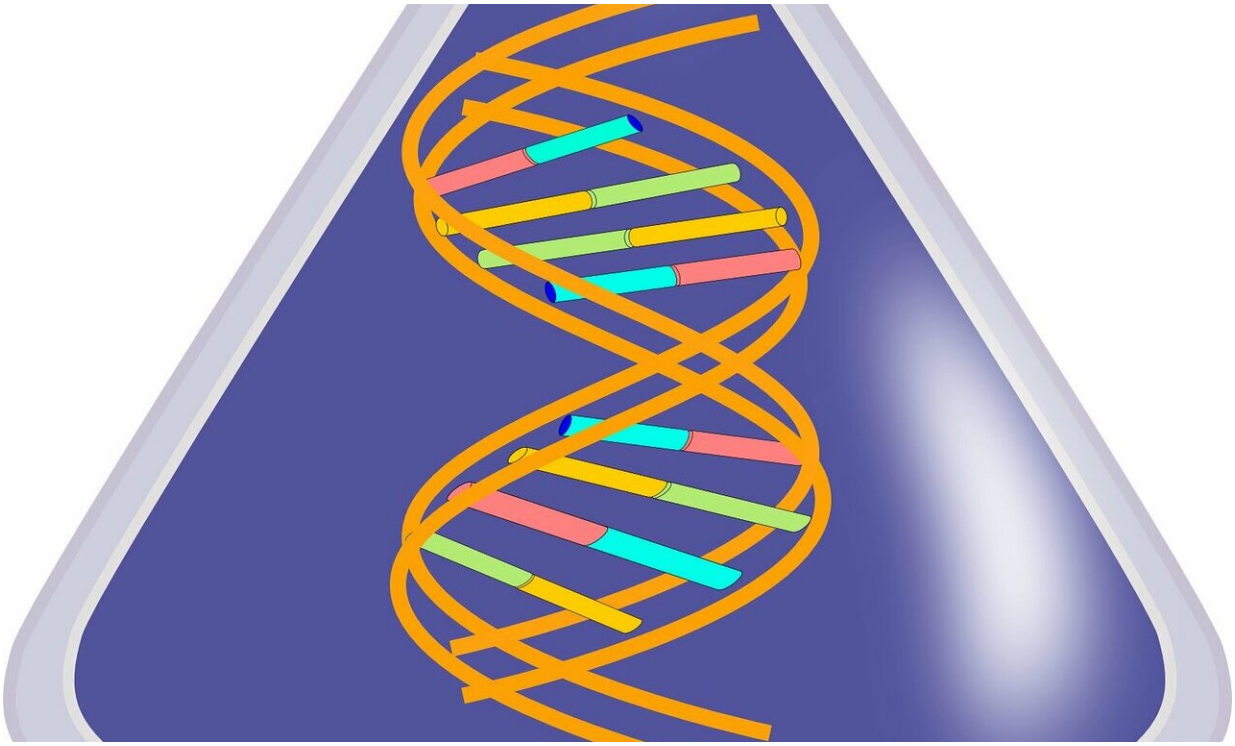

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A tiny molecule of RNA—known as 'micro RNA' - plays a key role in 'rewiring' cancer cells so they can resist the effects of chemotherapy, a new study reveals.

The discovery opens up the possibility of creating new cancer drugs that

target this micro RNA molecule, rather than more conventional treatments that block the action of proteins.

Scientists at The Institute of Cancer Research, London, found that a type of micro RNA known as MIR1249 plays a key role in allowing bile duct cancers to resist chemotherapy.

Micro RNAs, unlike other forms of RNA, don't help to translate the DNA code into proteins, but instead seem to be crucial for controlling the signalling networks within cells.

The researchers hope that MIR1249 could be a potential target for new drugs in bile duct cancer that could make chemotherapy much more effective. Bile duct cancer is very hard to treat and there is an urgent need to develop new therapies.

The researchers also believe that this mechanism driving resistance may be shared with other cancer types—raising the possibility that drugs to counteract it could have wider benefits.

The study is published in the journal *Hepatology* and released today (Wednesday) on Bile Duct Cancer Awareness Day. It was funded by The Institute of Cancer Research (ICR) as well as the European Union, Cancer Research UK, Pancreatic Cancer Action and the Italian Foundation for Cancer Research AIRC.

The study reveals that MIR1249 is able to 'rewire' the so-called WNT signalling network, which plays an important role in some healthy cells, and can be co-opted by cancer cells.

The WNT network is involved in the upkeep of stem cells—cells with the ability to self-renew and develop into many different cell types.

But when rewired, it seems to give cancer cells the features of stem cells, allowing them to become more resistant to treatment and able to survive the onslaught of chemotherapy.

The study, which involved mice and human tissue samples, revealed that by blocking MIR1249 activity, cancer cells became more sensitive to chemotherapy and responded better to treatment.

The researchers also found that 41 per cent of bile duct cancers had increased levels of MIR1249, suggesting it could be playing an important role within these tumours. In support of this idea, MIR1249 was also statistically associated with poorer survival outcome.

The next step will be to create drugs that could act against MIR1249, with the aim of preventing cancers from developing drug resistance and resensitising them to chemotherapy.

The ICR—a charity and research institute—is focused on understanding and combating cancer's ability to evolve and become drug resistant. It has less than £10 million still to raise for a new Centre for Cancer Drug Discovery, which will house an ambitious 'Darwinian' drug discovery programme to create new anti-evolution treatments.

Study leader Dr. Chiara Braconi, who carried out the research as Clinician Scientist at The Institute of Cancer Research, London, and is now Lord Kelvin Adam Smith Reader in the Institute of Cancer Sciences at the University of Glasgow, said:

"Our study shows the crucial role played by a piece of micro RNA in rewiring the network of signals within cancer cells and helping them to resist the effects of chemotherapy. It identifies MIR1249 as a potential drug target in bile duct cancers and possibly other tumour types, and opens up what could be an exciting new avenue of treatment.

"It's remarkable how such a tiny piece of RNA can play such a significant role in rewiring cancer cells so that they can resist chemotherapy. There is growing interest in the idea of developing drugs against RNA rather than against proteins, as studies like ours show the important role of micro RNA in cell signalling."

Study co-author Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"Bile duct cancer is becoming increasingly common around the world and survival rates are very poor, so there is an urgent need to develop better therapies for people with advanced disease whose treatment stops working. This new study shows the potential of targeting molecules called micro RNAs as a new form of treatment for drug-resistant cancers.

"At the ICR, we believe overcoming cancer evolution and drug resistance is the biggest challenge we face today in the field of cancer research. Through our new Centre for Cancer Drug Discovery, we are aiming to find new 'anti-evolution' treatments that can offer long-term control or cure even for advanced cancers."

Sal Cheema, 42, from Uxbridge, who was diagnosed with stage 4 bile duct cancer in 2018, said:

"I had chemotherapy for eight months which kept my cancer at bay. But within six weeks, I was devastated to learn that the cancer had spread to my lymph nodes.

"Bile duct cancer is rare, yet the incidence is increasing and it's not known why. This cancer is also affecting younger people more and more, so it's imperative that this specific research continues—not only for bile duct but other cancers too.

"There are very few treatment options for bile duct cancer patients, so I'm elated to hear of this research and discovery as it could open up a whole new way of targeting the cancer. More targeted treatments with fewer side effects are vital—these findings are very promising for people like me."

More information: Pietro Carotenuto et al, Modulation of biliary cancer chemo-resistance through microRNA-mediated rewiring of the expansion of CD133+ cells, *Hepatology* (2019). DOI: 10.1002/hep.31094

Provided by Institute of Cancer Research