Blocking Ran protein reverses resistance of lung and breast cancers

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This is Professor Mohamed El-Tanani, University of Bradford. Credit: Mohamed El-Tanani

Researchers at the University of Bradford have discovered a way to

prevent chemotherapy resistance in lung cancer by blocking a protein found in cancer cells.

Suppressing this protein, called Ran-GTP, also causes cancer cells already resistant to the first-line chemotherapy treatment, gefitinib, to become re-sensitised to the drug.

The research, led by Professor Mohamed El-Tanani, at Bradford's Institute of Cancer Therapeutics in collaboration with Queen's University Belfast, also found that Ran-GTP could be used to predict prognosis in breast cancer patients.

Key to the findings - published today (04 October) in *Oncotarget* - is the relationship between Ran-GTP and another protein called c-Met, which has previously been linked to several cancers. Overexpression of c-Met is known to cause chemotherapy resistance in breast and lung cancer and drugs which inhibit its activity are currently undergoing clinical trials for treatment of lung cancer. Professor El-Tanani believes the new research shows that targeting Ran-GTP could be a more effective approach.

"Much is known about the activity of c-Met and its impact on cancer, but our research is looking at things a step earlier, by focusing on the protein that regulates c-Met - Ran-GTP," he says. "c-Met needs Ran-GTP to function, and in particular needs very high levels when it becomes over-expressed or mutates - as is the case in cancers. By blocking Ran-GTP, we were able to both undo the resistance caused by c-Met and prevent that resistance occurring. This shows that Ran-GTP could be a good therapeutic target for cancer treatment, particularly in lung and breast cancer."

High levels of c-Met in breast cancer tumours are generally accepted to be associated with poor survival, but the team made a further unexpected discovery. When they analysed tissue samples from 247 breast cancer

patients, they found that patients with poor prognosis had tumours with high levels of both Met and Ran-GTP, rather than Met alone.

"This finding emphasises how the role of Ran-GTP, rather than the expression of c-Met alone, seems to be key to the progression of cancer," says Professor El-Tanani. "Even when c-Met was high and Ran was low, a patient's prognosis was much better. This means we might be able to use Ran levels to stratify patients to determine the most appropriate treatment, intervening with more aggressive treatments only in patients with high levels of both proteins. "

Although this study silenced Ran-GTP in lung cancer cells through genetic manipulation in the laboratory, the research team is already well down the road to finding a drug compound that can perform the same function.

"We've already screened millions of potential compounds that have the potential to inhibit Ran to find the most potent one in vitro and in vivo model systems as a preclinical validation," says Professor El-Tanani. "We now have two very strong candidates ready to move forward into clinical trials."

One candidate is a 'repurposed' drug that has been already pre-clinically validated in breast and lung cancer and is ready for clinical trials. As an existing drug, it's already known to be safe for use in humans and could be taken straight to Phase 2 trials. The second candidate is a peptide which has already been tested in animal models.

The University of Bradford is actively seeking further funding and investor support, and once secured, clinical trials for the two drug candidates could start within a few months.

"It's been a long road to get to this stage, but we're very excited about the

clinical potential for Ran-GTP inhibitors," he says. "It would be wonderful to see new treatments that block this protein enter trials, hopefully prove their effectiveness in treating cancer and eventually reach the clinic."

Catherine Pickworth, Cancer Research UK's science information officer, said: "When cancer becomes resistant to chemotherapy it's a lot harder to treat. Excitingly, this study has identified a potential target to stop or even reverse cancer resistance to a chemotherapy drug called gefitinib. Now more research and clinical trials are needed to find and test a drug that will help patients whose cancers have become resistant to chemotherapy."

Provided by University of Bradford