Cancer 'signature' first step toward blood test for patients

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Dr Sarah Best (left) and Dr Kate Sutherland from the Walter and Eliza Hall Institute, Melbourne, led a team that revealed a unique molecular signature in the blood that could be used to detect aggressive lung cancers with a simple blood test and identify patients who will respond to immunotherapies. Credit: Walter and Eliza Hall Institute

A discovery by Melbourne researchers could help to identify patients with a particularly aggressive type of lung cancer that are likely to respond to immunotherapies currently used in the clinic to treat other cancers.

The research has also revealed a unique molecular signature in the blood that could, in the future, be used to detect these aggressive lung cancers with a simple blood test.

Walter and Eliza Hall Institute cancer researchers Dr Sarah Best and Dr Kate Sutherland led the research, working with colleagues at Metabolomics Australia at the Bio21 Institute, University of Melbourne. The study was published today in *Cell Metabolism*.

The study focused on the role of two cell signalling pathways - KEAP1/NRF2 and PI3K - which are known to be involved in human lung cancers called adenocarcinomas.

"More than one in five lung adenocarcinomas have alterations in the KEAP1/NRF2 pathway, suggesting it is a major cancer driver," Dr Sutherland said. "These cancers are very aggressive, are resistant to standard therapies and have a poor prognosis, so new therapies are urgently needed."

Adenocarcinoma accounts for around 40 per cent of lung cancers and is often associated with a history of smoking, but is also the most commonly diagnosed lung cancer in non-smokers. It occurs more frequently in females and in young people than other types of lung cancer.

Dr Best said their study revealed that the tumours had characteristics indicating they were likely to respond well to immunotherapy.

"This is extremely important because these tumours are chemotherapy and radiotherapy resistant, meaning there are effectively no current treatments for these patients," Dr Best said.

"Using preclinical models, we showed for the first time that these tumours have the 'markers' that respond to anti-PD-1 and anti-CTLA-4 immunotherapies, which are some of the most exciting new cancer therapies being investigated in the clinic.

"But more importantly, we showed that these immunotherapies were effective in fighting the tumours and leading to tumour regression in our preclinical models."

Dr Best said the research showed that non-stop signalling caused by mutations in the KEAP1/NRF2 and PI3K pathways caused lung adenocarcinomas to develop.

"This is the first time anyone has shown that these alterations directly cause lung adenocarcinomas. With this knowledge, we can further investigate how targeting those pathways could lead to therapies for these aggressive and hard-to-treat cancers," she said.

Dr Sutherland said the unique molecular signatures found in the blood could be a tool to identify patients who would respond to immunotherapies, or even as an early detection test for these cancers.

"Working with our colleagues Dr David De Souza and Professor Malcolm McConville at Bio21 Institute, we were able to identify a unique 'breadcrumb' trail that the cancers leave behind in the blood," Dr Sutherland said.

"Our hope would be that the test could identify patients likely to respond to immunotherapies, but also that it could be a simple, non-invasive

blood test for the early detection of these lung cancers.

"The next steps would be to analyse human samples to prove the same is true in lung adenocarcinoma patients, but we need more funding for that work to continue and to generate results that will lead to better detection and treatments for the community."

Provided by Walter and Eliza Hall Institute