Same but different—unique cancer traits key to targeted therapies

September 13 2019

Dr Sarah Best (left) and Dr Kate Sutherland (right) from the Walter and Eliza Hall Institute in Melbourne, Australia, have shown that co-existing mutations in KRAS-positive lung cancers can give the tumour distinctive characteristics which they have successfully targeted to inhibit cancer growth. The study suggests this tactic should be investigated for targeted treatment of KRAS-positive human lung adenocarcinomas. Credit: Walter and Eliza Hall Institute

Melbourne researchers have discovered that the key to personalised therapies for some types of lung cancers may be to focus on their differences, not their similarities.

More than one in three lung cancers called adenocarcinomas have a common-cancer causing mutation in the gene KRAS, which is a potent cancer driver. Yet decades of attempts to develop a therapy that targets this gene have been unsuccessful.

Now scientists from the Walter and Eliza Hall Institute have shown that co-existing mutations in these cancers can give the tumour distinctive characteristics which they have successfully targeted to inhibit cancer growth. The study suggests this tactic should be investigated for targeted treatment of KRAS-positive human lung adenocarcinomas.

Targeting tumour traits

Lung cancer researchers Dr. Kate Sutherland and Dr. Sarah Best from the Walter and Eliza Hall Institute led the research, which was published today in the journal *Nature Communications*.

Dr. Best said the researchers were surprised to find that co-existing mutations could play such a significant role in the characteristics of some lung cancers. "In this study, we showed that KRAS-positive lung adenocarcinomas looked and behaved very differently depending on co-existing mutations in the tumour," Dr. Best said.

"Cancers with a co-mutation in the gene TP53 were flooded with immune cells, while tumours with a co-mutation in the gene KEAP1 changed their metabolism, how they make energy to fuel the tumour cell. We exploited these unique tumour traits, either by depleting the immune cells in tumour tissue or blocking the energy-producing machinery, and this proved effective in inhibiting tumour progression."

Targeted therapies to deplete immune cells or inhibit metabolic machinery were being explored in human trials for other types of cancers, Dr. Best said. "Our study suggests that some patients with KRAS-positive lung adenocarcinomas could benefit from targeted therapies that exploit the differences, rather than the similarities, in these tumours. This could make a real difference for patients with these lung cancers."

Targeted treatments a game-changer

In the past few decades, there has been an explosion in the development of targeted therapies for cancer. Targeted cancer therapies have transformed treatment and survival for people with diseases including breast, blood, skin and bowel cancers.

Unfortunately for people with KRAS-positive lung cancers, targeted therapies have been elusive said Dr. Sutherland.

"Researchers and pharmaceutical companies have been searching for decades for an effective therapy that targets KRAS, but have been unsuccessful. KRAS is considered 'undruggable' so we decided to look for alternative ways of attacking these cancers based on other tumour traits," Dr. Sutherland said.

Dr. Sutherland said understanding the nuances in tumour development was very important when trying to develop personalised therapies. "Our study suggests that a one-size-fits-all therapy would not be effective for all people with KRAS-positive lung cancers," she said.

A unique approach

The researchers studied the cancers in preclinical models and confirmed

the findings in donated human lung cancer tissues from patients, in collaboration with Associate Professor Gavin Wright from St Vincent's Hospital.

"We are confident that our models reflect what is happening in patients. And the benefit of the models is that they can be used for preclinical testing of potential therapeutics, to evaluate if they show promise for treating patients," Dr. Sutherland said.

More information: *Nature Communications* (2019). DOI: 10.1038/s41467-019-12164-y

Provided by Walter and Eliza Hall Institute