Breaking the genetic resistance of lung cancer and melanoma

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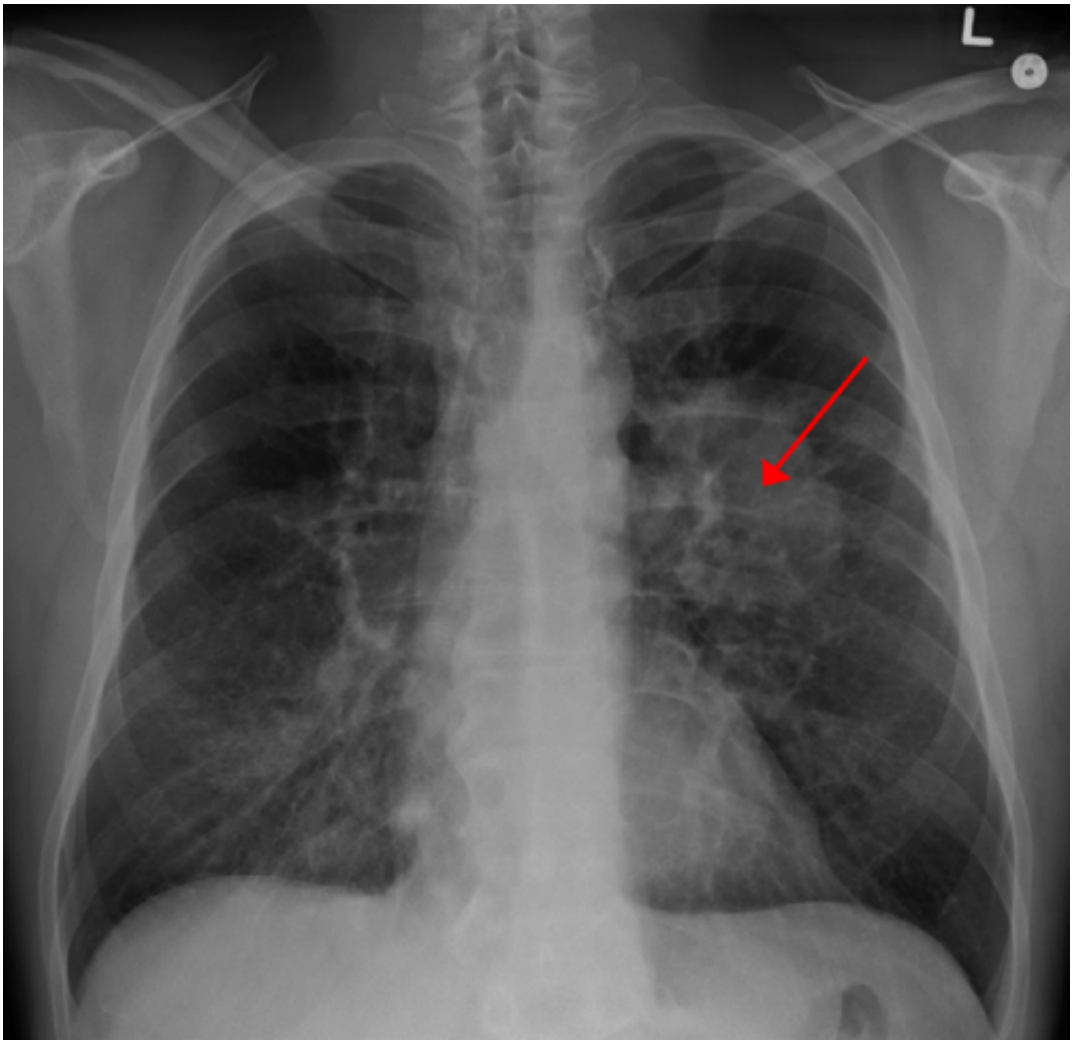

Lung CA seen on CXR. Credit: CC BY-SA 4.0 James Heilman, MD/Wikipedia

Researchers from Monash University and the Memorial Sloan Kettering Cancer Center (MSKCC, New York) have discovered why some cancers – particularly lung cancer and melanoma – are able to quickly develop deadly resistance to targeted therapies.

Dr Luciano Martelotto, from the Monash University Faculty of Medicine, and his collaborators Dr Piro Lito and Yaohua Xue (MSKCC), have performed intricate DNA sequencing tests on single cells using genetic models of lung cancer and melanoma.

Lung cancer and melanoma are amongst the hardest to treat of the cancers because of their capacity to alter their genetics, developing resistance to targeted therapies. In a paper published today (TBC) in *Nature Medicine*, the researchers used animal models from tumours derived from patients and single-cell genomics to develop a hypothetical model of resistance, called "fitness threshold model," that explains why and how resistance to therapy occurs in these cancers, and identified types of therapies to prevent this process from occurring.

Lead author Dr Martelotto said that until now, the way that these tumours respond and become resistant to targeted therapies has been poorly understood.

"For the first time, we've demonstrated that solid tumours like melanoma and lung cancers can grow back shortly after therapy, but when they do they are made of genetically diverse sub-groups of malignant cells—and, scarily enough, all of these are resistant to treatment. This genetic diversity is what allows the cancers to adapt to the treatment and resist it." Dr Martelotto explains.

The research team's fitness threshold model links the effect of a given drug with the selection of resistance-causing alterations in DNA, resulting in significant implications for the treatment of cancer patients.

Dr Martelotto said that these findings are important for oncologists and patients because they show that the way that drugs are administered during therapy can have a critical impact on the outcome of the response to treatment.

"In our work, we showed that intermittent administration enables simultaneous delivery of multiple targeted therapies while maintaining lower toxicity, and our fitness threshold model explains how other resistance-causing alterations may develop during targeted therapy," Dr Martelotto said.

This important finding sheds light on the development of new therapeutic designs to more effectively treat patients.

More information: Yaohua Xue et al. An approach to suppress the evolution of resistance in $BRAF^{V600E}$-mutant cancer, *Nature Medicine* (2017). DOI: 10.1038/nm.4369

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