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Scientists fingerprint single cancer cells to map cancer's family tree

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A new method to take the DNA fingerprint of individual cancer cells is uncovering the true extent of cancer's genetic diversity, new research reveals.

The technique can identify the founding mutations from which a tumour evolved and then uses computer software to draw a map of the cancer's family tree.

Scientists at The Institute of Cancer Research, London, and the Wellcome Trust Sanger Institute used DNA sequencing to identify a panel of mutations present across thousands of cancer cells in three patients with leukaemia. They then tested hundreds of individual cancer cells for each of the mutations to determine their genetic fingerprint and place them into cancer's family tree.

The study found that each patient's cancer had a distinct family tree, with a unique series of mutations driving their growth.

The findings could be used to identify the key mutations that occur early in the development of tumours, allowing doctors to use targeted treatments more effectively.

The study, published in the journal *Genome Research*, was funded by Leukaemia and Lymphoma Research, the Kay Kendall Leukaemia Fund, The Institute of Cancer Research (ICR), and the Wellcome Trust.

Tumours grow through a process of Darwinian evolution, where cancer cells develop an advantageous mutation that allows them to survive and multiply, producing a population of cells which can mutate further.

Sequencing the whole genome of a cancer provides a tally of the many mutations that accumulate within it, but can fail to identify where mutations have branched off the evolutionary tree to produce distinct sub-populations of cells.

Targeted cancer treatments are designed to attack molecules produced by mutations, but if the targeted mutation occurs on an evolutionary branch and not the trunk, the treatment will fail as other branches dominate and treatment resistant cells spread.

The new technique used software to assign the cancer cell with the fewest mutations as the ancestral clone and place it at the root of the evolutionary family tree, with the other clones arranged as branches above it.

Professor Mel Greaves, Professor of Cell Biology at The Institute of Cancer Research, said:

"The diversity of genetics within individual cancers reveals the otherwise hidden evolutionary histories of cancer cells. Our research highlights how mutations distribute into branching patterns that are unique to each patient. The diversity of these evolutionary tree structures helps explain why advanced cancer can be so resilient to treatment."

Professor Alan Ashworth, Chief Executive of The Institute of Cancer Research, said:

"The evolution of resistant cancer cells can be a problem for targeted therapy. If we can understand how this happens we may be able to devise

better methods of treatment that slow or avoid relapse after treatment."

Dr Elli Papaemmanuil from the Cancer Genome Project at the Wellcome Trust Sanger Institute said: "Single cell genomics, the genetic study of individual cells, is becoming increasingly important for cancer research. It allows us to decipher the order and timings of mutation acquisitions, as well as providing insights into the biological mechanisms or exposures that result in mutations."

Professor Chris Bunce, Research Director at Leukaemia & Lymphoma Research, said: "We are beginning to understand how unique and complex each patient's cancer is and the profound implications that this can have on the success of treatment. By cataloguing the variety of genetic faults found in hundreds of individual leukaemia cells in each patient, this study significantly advances our understanding of how cancers start and evolve. The efficient and accurate methods developed could be used in leukaemia and other cancers to predict how an individual's disease will progress, guide the personalised choice of treatment to target cancer at its root and monitor the risk of it coming back."

More information: Potter NE, Ermini L, Papaemmanuil E, Cazzaniga G, Vijayaraghavan G, Titley I, Ford A, Campbell P, Kearney L, Greaves M. Single cell mutational profiling and clonal phylogeny in cancer. Genome Res in advance September 20 2013, DOI: 10.1101/gr.159913.113

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