CRISPR catches out critical cancer changes

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In the first large-scale analysis of cancer gene fusions, which result from the merging of two previously separate genes, researchers at the Wellcome Sanger Institute, EMBL-EBI, Open Targets, GSK and their collaborators have used CRISPR to uncover which gene fusions are critical for the growth of cancer cells. The team also identified a new gene fusion that presents a novel drug target for multiple cancers, including brain and ovarian cancers.

The results, published today (16 May) in *Nature Communications*, give more certainty for the use of specific gene fusions to diagnose and guide the treatment of patients. Researchers suggest existing drugs could be repurposed to treat some people with pancreatic, breast and lung cancers, based on the gene fusions found in their tumours.

Gene fusions, caused by the abnormal joining of two otherwise different genes, play an important role in the development of cancer. They are currently used as diagnostic tools to predict how particular cancer patients will respond to drugs, as well as prognostics, to estimate the outcome for a patient given the best possible care. They are also the targets of some of the latest targeted treatments for cancer.

Researchers have identified around 20,000 gene fusions so far, however their exact function and role in developing cancer remains poorly understood. Discriminating between fusions that have a role in cancer survival and those that do not has important clinical implications.

In the first large-scale study of gene fusion function, researchers at the Wellcome Sanger Institute, EMBL-EBI, Open Targets, GSK and their collaborators analysed more than 8,000 gene fusions in over 1,000 human cancer cell lines, from 43 different cancer types, including paediatric cancers and cancers with unmet clinical need.

The team tested the cell lines against more than 350 anti-cancer drugs to see which existing drugs could be repurposed to potentially treat cancer patients with gene fusions, and employed CRISPR as a tool to discover which key gene fusions are critical for cancer cell survival.

The team found that 90 per cent of gene fusions do not play an essential role in cancer. These results should be considered when inferring causes of cancer from the genome sequence of patients' tumours.

Dr. Gabriele Picco, co-first author from the Wellcome Sanger Institute, said: "The majority of gene fusions are not essential for the survival of cancer cells. As genome sequencing patients' tumours becomes more common, those interpreting the data must be careful when considering whether a particular gene fusion is driving the cancer."

Researchers also discovered a new fusion, YAP1-MAML2, which is essential for the progression of multiple cancer types, such as brain and ovarian cancers.

Dr. Mathew Garnett, lead author from the Wellcome Sanger Institute and Open Targets, said: "We discovered a handful of gene fusions that are key for cancer survival. These genetic changes may present opportunities for treating patients with existing drugs, or could be the drug targets of the future. We discovered a new gene fusion, YAP1-MAML2, which offers a new drug target for several cancers, including ovarian cancer."

The results also suggest that gene fusions involving RAF1, ROS1 and BRD4 could be targeted by existing drugs, meaning new treatment options may be available for patients with rare sub-types of pancreatic, breast and lung cancers.

Dr. Julio Saez-Rodriguez, previously from EMBL-EBI and Open

Targets, and now based at Heidelberg University, said: "Cancers differ between people and having a genomic view of these differences is increasing our understanding of cancer and opening up treatment options for patients. This study offers further opportunities to employ gene fusions as therapeutic biomarkers and stratify patients onto clinical trials, potentially offering more targeted and effective clinical studies."

The collaboration between researchers at Sanger, EMBL-EBI and GSK, the Open Targets partners, bolster the translation of these research results into new treatments.

This research contributes towards building the Cancer Dependency Map, a rulebook for the precision treatment of cancer in the future.

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