Genomic fingerprint can highlight which breast, ovarian, pancreatic and gastric cancers likely to respond to treatment

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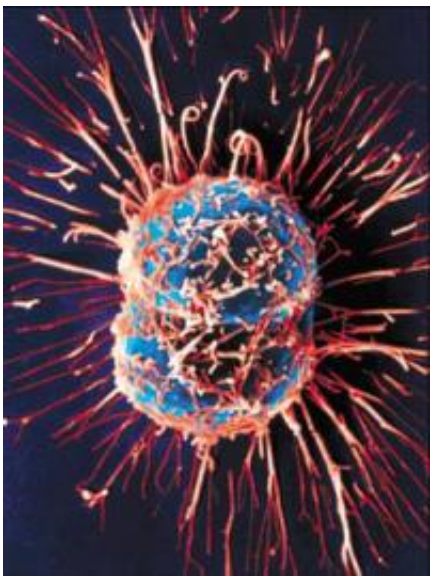

Dividing Cancer Cells. Credit: University of Birmingham

Gastric cancer, otherwise known as stomach cancer, does not respond well to existing treatments and it is currently the third leading cause of cancer death in the world (after lung and liver cancer). Researchers have discovered that certain drugs, currently used to treat breast, ovarian and pancreatic cancers, could also be used to treat certain gastric cancers with a particular pattern of mutations (genomic molecular fingerprint).

Recent research has shown that a specific genomic molecular fingerprint , called signature 3, is associated with cells that have defective DNA repair mechanisms, for example due to faulty BRCA1 or BRCA2 genes which are linked with breast cancer. Cancer cells harbouring signature 3 have defects that stop them from efficiently repairing damage to their DNA. Due to their inability to repair DNA damage, these cells become vulnerable to platinum drugs and PARP inhibitor drugs, both of which attack DNA, causing it to break. Since the DNA damage cannot then be repaired, the cancer cell dies.

Signature 3 could therefore predict which cancers would be likely to respond to particular drug therapies. Initially found only in some breast, ovarian and pancreatic cancers, signature 3 may be present in other human cancers, and researchers in this latest study aimed to find out which other cancers harboured this clue to drug vulnerability.

"We analysed the cancer genomes of 10,250 patients, performing a large-scale computational screen across 36 different types of tumours, looking for the pattern of Signature 3 in each sample. Not only did we confirm the presence of signature 3 in a significant percentage of breast, ovarian, and pancreatic cancers, we also found this molecular fingerprint in approximately 10% of stomach cancers," said Dr Ludmil Alexandrov, corresponding author and Oppenheimer Fellow at Los Alamos National Laboratory in the USA. "This subset of stomach cancer is likely to have a defective DNA break-repair mechanism, and could therefore be susceptible to existing treatments such as platinum drugs or PARP inhibitor drugs."

In addition to discovering the pattern of signature 3 in gastric cancer, the study quantified its occurrence in other cancer types. It showed that 30% of ovarian, 27% of breast and 8% of pancreatic cancers exhibit this molecular fingerprint, a higher percentage than originally thought. Previous research using whole genome sequencing data showed that

pancreatic cancers harbouring the signature 3 fingerprint responded very well to platinum therapy. This suggests that the presence of signature 3 could be used as a biomarker to guide targeted therapy for not just some gastric cancers, but also for breast, ovarian and pancreatic cancers.

Previous research has shown the importance of two genes, BRCA1 and BRCA2 to breast and ovarian cancer and currently, clinicians target platinum therapy or PARP inhibitor drugs towards breast and ovarian cancer patients who have mutations in their BRCA1 and BRCA2 genes. However, this study shows that these two genes are only part of the story.

"While all the patients with BRCA1 and BRCA2 mutations show this signature 3 fingerprint, there are also many patients who have signature 3 but don't have mutations in BRCA1 and BRCA2. By focusing exclusively on those two genes, clinicians may be missing many cancer patients with the genomic signature 3 who could benefit from PARP inhibitor drugs or platinum therapy." Says Professor Suet Yi Leung, Chair of Gastrointestinal Cancer Genetics and Genomics from the University of Hong Kong "Even just for breast cancer, you could potentially double the population size that could be treated with this therapy."

PARP inhibitor drugs shut down a specific DNA repair enzyme, poly ADP ribose polymerase, and because they are more targeted, they cause far fewer side effects than platinum drugs. Olaparib (trade name Lynparza) is the latest PARP inhibitor drug to be licenced for use against ovarian cancer, but using Signature 3 as a marker, this and future PARP inhibitor drugs could be used to treat other cancer types such as gastric cancers. This would allow doctors to treat more patients, more effectively.

So far, this has only been shown in a laboratory setting using genomics. The next steps would be to clinically test these therapies to see if patients

with cancers that have the signature 3 molecular fingerprint really do respond as hoped to these treatments. It takes many years of research to launch a new drug as not only does any new treatment have to be effective, it also has to be proven to be safe in humans. However, PARP inhibitors are already available and safety tested, which could speed up the process of approving their use for other cancers.

"This is an extremely exciting finding which shows the importance of genomic sequencing for personalised healthcare in the future." says Professor Michael Stratton, corresponding author and Director of the Wellcome Trust Sanger Institute. "In years to come, routine genomic analysis of cancers could show which have the signature 3 fingerprint and inform and transform treatment of thousands of patients with these specific breast, ovarian, pancreatic and gastric cancers."

More information: Alexandrov LB et al., (2015) A mutational signature in gastric cancer suggests therapeutic strategies. *Nature Communications* 2015. DOI: 10.1038/ncomms9683

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