Exploiting the Cancer Genome for Personalised Therapies

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Scientia

EXPLOITING THE CANCER GENOME FOR PERSONALISED THERAPIES

The effectiveness of cancer treatments could be hugely improved by a greater understanding of the cancer genome. This is the focus of the work of **Dr John Paul Y.C. Shen**, MD, of the University of Texas MD Anderson Cancer Center, who is creating comprehensive molecular 'maps' of cancer cells and their interactions. Understanding cancer at a molecular level is the first step towards Dr Shen's very real hope of bringing personalised cancer treatments into the clinic.

From Laboratory to Clinic

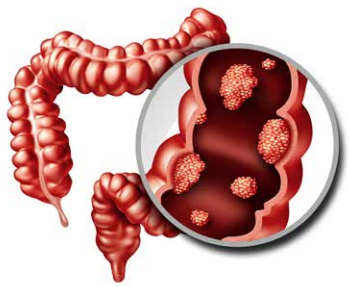
Cancer is the result of an accumulation of mutations that lead to uncontrolled cell growth, and so it makes sense that a better understanding of these genes could lead to an improvement in cancer treatments. A cell's complete set of genes is known as its genome, and for Dr John Paul Y.C. Shen, MD, a fuller understanding of the cancer genome is paving the way for delivering more effective chemotherapies in practice. Dr Shen is a physician-scientist at the University of Texas MD Anderson Cancer Centre, where he is an Assistant Professor in the Department of Gastrointestinal Medical Oncology and heads a research laboratory of experimental and computational scientists developing targeted cancer treatments.

Dr Shen aims to understand cancer on a molecular level and then transfer this knowledge to the clinic, facilitating the prediction of which chemotherapy will work for each patient. As a physician, Dr Shen treats patients with malignancies of the gastrointestinal tract including colon (colorectal) and appendix (appendiceal) cancers. His research aims to combat two major limitations that are faced in this field: a general lack of targeted therapies, and a lack of predictive biomarkers indicating which therapy a patient is likely to respond to. And it is working! So far, work in Dr Shen's laboratory has contributed to three clinical trials of novel drugs which have the potential to directly benefit the lives of colorectal and appendiceal cancer patients.

A Synthetic-Lethal Gene Pair

The major pitfall of traditional, also called cytotoxic chemotherapies is that in addition to cancer cells, they attack other rapidly growing cells in the body, such as those found in hair roots. Consequently, hair loss, nausea and vomiting, and decreased blood counts are among the many unpleasant side effects faced by cancer patients while undergoing treatment. This problem can potentially be overcome through the use of drugs which selectively target cancer cells while sparing normal cells, in a process known as 'synthetic lethality'.

Synthetic lethality depends on the phenomenon that two independent



gene mutations can cause an unexpected characteristic to arise in a cell, that is unrelated to either original gene. When this occurs, it is indicative of both original genes being part of the same biological process or pathway. Thus, damaging the two genes may result in a dramatic change, such as cell death, while damaging only one will not. The two genes are then termed a 'synthetic-lethal' gene pair.

The cancer drug Olaparib exploits this concept. Developed in 2014, it is effective against ovarian, fallopian tube, and peritoneal cancers, which share a common BCRA gene mutation. Olaparib targets the other gene in BCRA's synthetic-lethal gene pair, resulting in the death of cancer cells while normal cells remain healthy.

Discovering other such lethal gene pairs presents a significant challenge, due to the complexity and variability of cancer cells' genetic interactions. In 2017, Dr Shen was part of a team that addressed this problem in a pioneering manner.

A Novel Gene Editing Approach

While a postdoctoral fellow in the University of California's Department of Medicine in his then-mentor's lab, Dr Shen helped to develop a novel method of searching for synthetic-lethal gene pairs. The technique, which was a novel application of the CRISPR/Cas9 gene editing process, resulted in over 120 potential new targets for cancer drugs.

CRISPR is a bacterial derived mechanism used in the laboratory to knock out target genes. It does this in two stages: first, DNA recognition processes lead to the location of a pre-determined target gene in the genome, and, second, a protein called Cas9 cuts the DNA, inducing a mutation which inactivates said gene. The organism's genes are therefore edited in a way that allows scientists to investigate the functions of particular genes of interest.

In this study, Dr Shen and his team used CRISPR to inactivate 73 genes in lab-cultured kidney cells, lung cancer cells, and cervical cancer cells, for testing a total of 150,000 unique gene interaction combinations. They then looked at the effects on cell growth, and ultimately uncovered 120 new synthetic-lethal interactions. This was the first time that such a low-cost and high-throughput approach had been carried out to make this discovery, and it presented opportunities both to gain a greater understanding of cancer development, and to develop new therapies.

Promises and Pitfalls of Synthetic Lethal Interactions

The marvellous opportunities presented by CRISPR screening for synthetic-lethal gene pairs are aided by decreased cost and increased throughput compared to previous methods. Synthetic lethal interactions fall into the growing field of precision oncology, as they overcome the difficulties faced by more traditional chemotherapies of damaging healthy cells. In the future, novel drug development must consider the source of cancer since many of the synthetic-lethal gene pairs were only fatal in one of the three cell types. Additionally, the team's findings must be validated in further cell types and mice models; this nevertheless presents a promising start to the development of more targeted cancer therapies.

Perhaps the greatest barrier faced by Dr Shen's work in developing synthetic-lethal therapies is the diversity of cancer at a molecular level. Even two seemingly identical tumours of the same type in different patients have vastly different genetic makeups; this is also true of different cells within the same single tumour. This explains why chemotherapy can never be 'one-size-fits-all', and why molecular profiling of patients' cancers is beneficial when planning treatment options. Along these lines, proposed novel cancer therapies must be heavily context specific.

Considering the complexities of the relationships involved, Dr Shen's team pointed out that in the development of new synthetic lethal drugs, it will be just as useful to know when a drug will not work, as it will be to know when one will. Patients will be genetically profiled to reveal any predispositions to certain drugs in a system which is already in

existence. During colorectal tumour diagnoses, patients are currently screened for mutations which correlate with a lack of response to anti-EGFR antibody treatments. Screening processes of the same kind could easily be applied to synthetic-lethal drug interactions.

The Genetic Landscape of Appendiceal Cancers

The cancer genome is incredibly complex and incompletely understood, and therefore, treatment guidelines are typically based on data from clinical trials. This presents an issue with rarer cancer types, including appendiceal cancer, where very little clinical trial data are available. Patients presenting with appendiceal cancers tend to receive treatment in the form of colorectal cancer chemotherapy regimens, despite the multitude of differences between the two types. Dr Shen aimed to remedy this through his 2018 molecular profiling of 703 different appendiceal cancer samples, which enabled the discovery of novel biomarkers for these elusive tumours.

Each cancer was sequenced and analysed for individual mutations, while looking for trends in the entire cohort that could help to guide treatment. The team found that appendiceal cancers had molecular profiles that were distinct from colorectal cancers, suggesting that their treatments should vary. In addition, two genes were identified as biomarkers for appendiceal cancer (TP53 and GNAS), which is significant due to their ease of detection. This comprehensive portrait of the genomic landscape of appendiceal cancer highlights the importance of the molecular profiling of cancers in order to discover new biomarkers and advance existing treatments. More directly, it will help with the development of future clinical studies in appendiceal cancer, to allow a more specific treatment approach going forward.

Paving the Way for Precision Medicine in the Treatment of Appendiceal Cancer

For Dr Shen, his work in the fight against cancer is just getting started. Despite research demonstrating the differences in tumour molecular profiles between the two, the practice of treating appendiceal cancer with colorectal cancer chemotherapies is likely to continue unless specific cancer treatments for the former are developed. Dr Shen's proposal illustrates his ambition to carry out a series of experiments that will provide a foundation for future drug developments that are specific to appendiceal cancers.

Dr Shen hopes to construct, characterise, and test preclinical models of appendiceal cancer to identify new drug targets in appendix cancer. He is also working to establish a database of appendix cancer mutation and transcription data, where patients could submit data on their own tumour in an anonymous fashion. By 'crowd-sourcing' the collection of appendix cancer data, he hopes to collect enough data to understand how appendix tumours differ from one another. Considering the ability of cross-interactions between seemingly unrelated genes to cause synthetic lethality, it is clear that cancer should be considered a network-based disease. However, traditional biological pathways are heavily rewired in cancer cells, and different tumour types contain unique genetic networks which are context specific.

This environmental specificity adds another layer of complexity, part of why Dr Shen is trying to generate more data from mouse models of appendix cancer where the tumours grow in the peritoneal cavity, which surrounds the intestines, similar to the usual spread of appendix cancer in humans. He is also working with collaborators to use automated intelligence (AI), also called machine learning, to help make predictions from this complex dataset. The end goal of identifying more effective appendiceal cancer therapies and/or predictive biomarkers will take years of dedicated effort, but meaningful progress is expected in the near future.

Meet the researcher

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Dr John Paul Y.C. Shen is a physician-scientist who received his MD from Washington University in Saint Louis in 2008, before undertaking clinical training at the University of California, San Diego in internal medicine, haematology, and oncology. He then completed a postdoctoral fellowship in cancer genomics under the mentorship of Professor Trey Ideker in 2018, alongside his career as a physician. Today, he works as an Assistant Professor in the Department of Gastrointestinal Medical Oncology and a Cancer Research and Prevention Institute of Texas (CPRIT) Scholar in Cancer Research at the University of Texas MD Anderson Cancer Centre, where he heads a laboratory of scientists studying the genomics of colorectal and appendiceal cancers. His long-term research goal is to better understand the cancer genome for the delivery of more effective chemotherapies. Among many other accolades and awards, in 2016 he was selected as a NextGen Star by the American Association for Cancer Research.

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FURTHER READING

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