Telomeres exposed

A new target for cancer diagnosis and treatment

- Telomeres cap and protect the ends of our genetic material – the chromosomes.
- Some cancer cells exploit the protective role of telomeres.
- Certain cancer treatments target the telomere's action – but are not always effective. Is there a way to detect and treat these cancers more effectively?
- Dong Zhang at New York Institute of Technology College of Osteopathic Medicine, USA, has found a way to accurately measure telomeres. Not only does his work allow for accurate cancer diagnosis, it also shows promise for personalised cancer treatment.

Ever wondered how your own DNA protects itself from the inevitable wear and tear associated with the relentless process of cell division? Telomeres, the repetitive DNA sequences at the ends of your chromosomes, serve as the guardians of genomic integrity, playing a crucial role in safeguarding the precious genetic information within your cells. Now, what happens once cancer cells exploit and manipulate this intricate process to their advantage, unlocking the secrets of replicative immortality? The question arises: Can we still beat cancer cells at their own game and harness this knowledge for our benefit?

First, let's dive into the world of telomeres. Telomeres are comprised of repetitive DNA sequences. They are specialised structures positioned at the ends of linear chromosomes. These chromosomes are thread-like structures composed of DNA and proteins, found within the nucleus of a cell, and serve as carriers of genetic information in the form of genes. Think of telomeres as protective caps, a bit like the plastic tips on shoelaces that prevent fraying. In the context of cellular processes, telomeres act as essential safeguards against the attrition of genetic material during cell division. In normal somatic cells (any cell in the body), telomeres are typically around 10–15 kilobases (kb) long. However, with each round of cell division, they naturally undergo shortening in the absence of a telomere maintenance mechanism (TMM). This gradual reduction in telomere length can eventually lead to cell cycle arrest, senescence, or even cell death.

Telomeres and cancer: Friend or foe?

In the case of cancer, cells are characterised by rapid and uncontrolled proliferation, while specific mechanisms are activated to counteract telomere shortening. There are two primary TMMs used by cancer cells: the reactivation of telomerase (TEL+), which gives the enzyme telomerase the green light to add telomeric DNA sequences to existing telomeres; and the adoption of the alternative lengthening of telomeres (ALT+) pathway, which relies on homology-dependent repair (HDR) to maintain their telomeres. This reliance on HDR can result in unique structural changes of telomeres. ALT+ pathway activation is more prevalent in certain types of cancers, such as neuroblastoma, pancreatic

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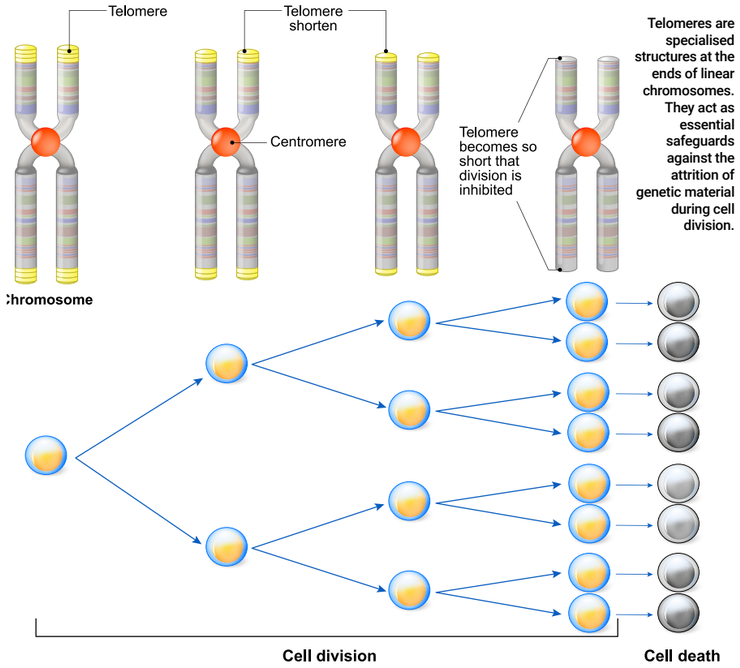
neuroendocrine tumours, osteosarcoma, and glioma. Approximately 10–15% of cancers do not exhibit detectable telomerase activity but maintain telomere integrity through the ALT pathway.

A single assay to spot the difference

Dong Zhang is an associate professor of cancer biology at the New York Institute of Technology College of Osteopathic Medicine, and the director of the Center for Cancer Research at the New York Institute of Technology, USA. His studies focus on understanding the distinct features of ALT+ cells (cells that use the ALT pathway) compared to TEL+ cells (cells that use the telomerase pathway). In particular, he hopes that this work could address the current limitations faced in treating ALT+ cancers. Unfortunately, while TEL+ cancers benefit from more effective and less toxic drugs, ALT+ cancers often require conventional chemotherapy, which tends to be less effective and is often toxic resulting in side effects. Addressing this issue is particularly challenging due to the intricate nature of detecting ALT activity.

Various assays have been used to detect and quantify telomere changes, but the single-molecule telomere assay via optical mapping (SMTA-OM) technology is a novel method that enables genome-wide analysis at the single-molecule level. This technology allows for the visualisation and quantification of telomeres, and associated features with high precision. In other words, it helps scientists to 'look' straight



Telomeres are specialised structures at the ends of linear chromosomes. They act as essential safeguards against the attrition of genetic material during cell division.

This innovative diagnostic tool enables single-molecule scrutiny of telomeres, paving the way for tailored treatment strategies.

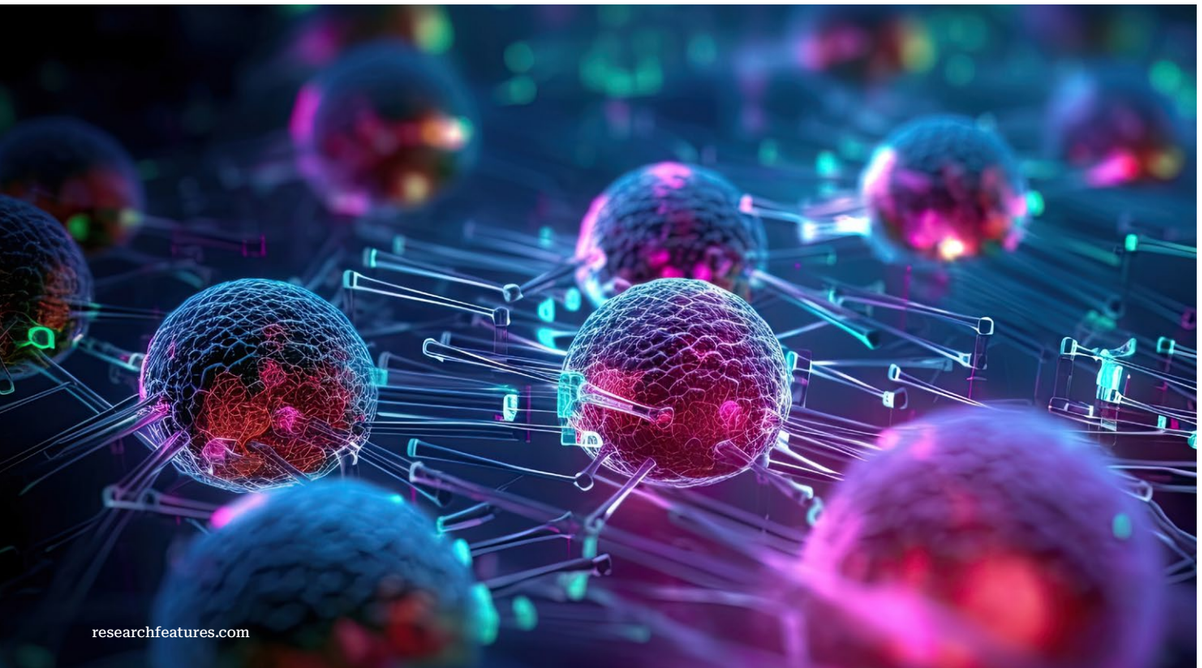
into the eyes of our genome and spot the telomeres. In close collaboration with Dr Ming Xiao at Drexel University, the group looked at various factors and discovered important differences between two types of cells, ALT+ and TEL+. In simpler terms, the study found unique traits in ALT+ cells, and even among them, each cell line had its own distinct features. Understanding these differences could help researchers tell apart different types of cancers, which is crucial for developing better treatments.

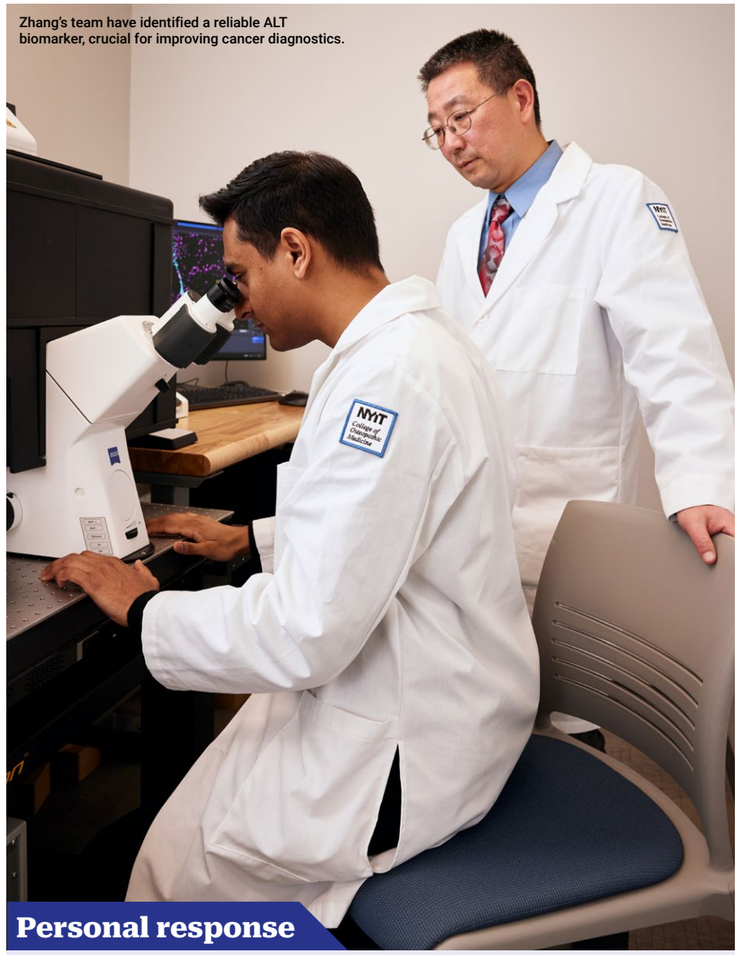
Paving the way for diagnosis and therapy

The groundbreaking SMTA-OM technology is set to transform cancer diagnosis and therapy. It allows for precise analysis of telomere features at the single-molecule level, offering a comprehensive understanding of characteristics unique to ALT+ cells. This innovation facilitates the identification of a reliable ALT biomarker, crucial for improving cancer diagnostics.

Alongside this, the researchers have identified a promising target, FANCM, associated with ALT+ cancers. FANCM serves as a potential focal point for therapeutic interventions. FANCM, or Fanconi Anemia Group M, is a protein involved in DNA repair processes and is associated with the Fanconi anemia pathway. The Fanconi anemia pathway is crucial for maintaining genomic stability by repairing DNA damage, particularly interstrand crosslinks. Mutations or dysregulation in genes related to this pathway can contribute to the development of various cancers. The group identified FANCM as a potential target for therapeutic interventions in the treatment of ALT+ cancers. Inhibiting FANCM could be a strategy to address the unique characteristics of ALT+ cancers, presenting an opportunity for targeted therapies. The ongoing development of FANCM inhibitors reflects a focused effort to translate this discovery into practical and targeted therapeutic solutions for ALT+ cancers.

The breakthrough discovery of molecular features in ALT+ cancers, paired with the precision of the SMTA-OM technology, advances personalised medicine. This innovative diagnostic tool enables single-molecule scrutiny of telomeres, paving the way for tailored treatment strategies. By pinpointing unique molecular aspects, it opens avenues for personalised interventions, promising more effective and targeted therapies for ALT+ cancers, heralding a new era in cancer care.





Zhang's team have identified a reliable ALT biomarker, crucial for improving cancer diagnostics.

Personal response

What are your expectations for the clinical application of your research findings, particularly in terms of personalised therapies for ALT+ cancers?

Using the SMTA-OM technology, we can identify the ALT-positive cancer with high confidence. Once we develop ALT inhibitors, like the FANCM inhibitors, when we treat the ALT+ cancer patients with them, we expect better efficacy with milder side effects.

How does the Single-Molecule Telomere Assay via Optical Mapping (SMTA-OM) technology work, and how could it be integrated into routine medical practices for cancer diagnosis?

SMTA-OM colour-codes telomeres based on their sequences and locations. In addition, SMTA-OM also colour-codes individual chromosome arms. Therefore, one of the most important advantages of SMTA-OM is to monitor the changes of telomeres and chromosome ends of individual chromosomes arms, which very few technologies can do. DNA needs to be extracted from tumour samples and used for the SMTA-OM.

If FANCM inhibitors are developed and used as a treatment, are there potential side effects that might need to be considered?

Many adult stem cells and germ cells express telomerase. As far as we know, there are very few normal cells, if any, including the stem cells, that use the ALT pathway. In addition, knockout of FANCM in mice does not seem to affect their viability. Therefore, we expect that FANCM inhibitors will have minimal damage to the normal cells, ie, milder side effects.

Considering the role of telomeres in various cellular processes, do you foresee potential applications of your research findings in areas beyond cancer, such as ageing-related diseases or regenerative medicine?

Yes. The integrity of telomeres also affects ageing, cardiomyopathies, and certain genetic diseases, including Duchenne syndrome and dyskeratosis congenita.

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Collaborators

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Bio

Dr Dong Zhang is an associate professor of Cancer Biology at the College of Osteopathic Medicine, New York Institute of Technology. He also serves as the director of the Center for Cancer Research at the New York Institute of Technology. Dr Zhang obtained his PhD degree in Biochemistry and Molecular Biology from Brandeis University in the laboratory of Nobel Laureate, Dr Michael Rosbash. Dr Zhang then did his postdoctoral training at the Biochemistry Department of Baylor College of Medicine and the Genetics Department of Harvard Medical School. In addition to running a cancer research lab, Dr Zhang also teaches medical biochemistry to medical students and is a faculty adviser for the first aid for the USMLE Step 1.

Further reading

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