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HKU and SZBL Scientists Discover First Human DNA-Cutting Enzyme That Senses Physical Tension – A Breakthrough in Understanding How Cells Prevent Genetic Disorders

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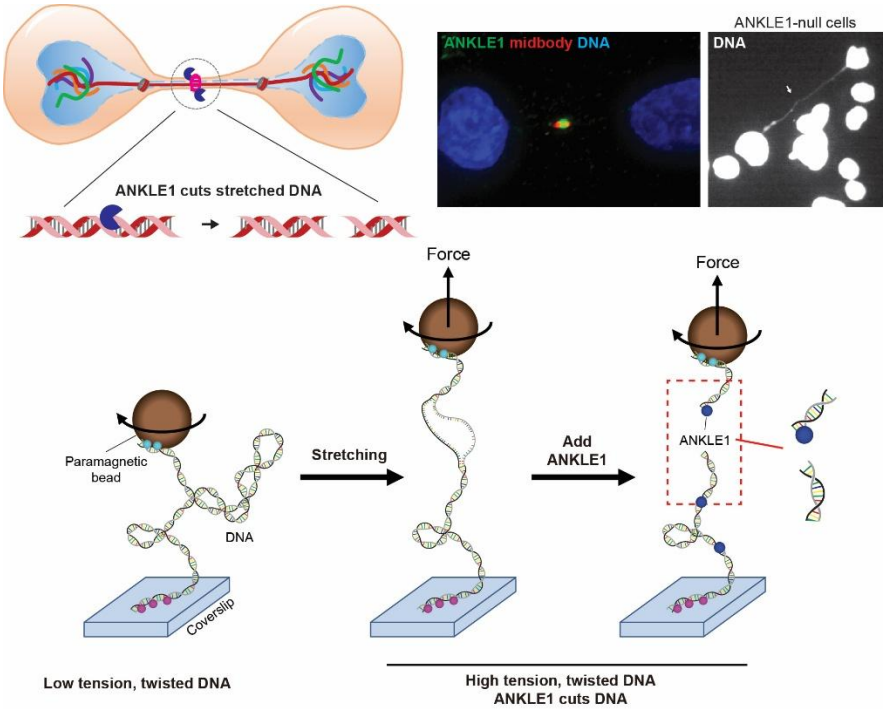

Figure 1. *ANKLE1 senses mechanical tension in DNA and helps resolve DNA bridges connecting separating daughter nuclei. ANKLE1 (green) localises to the midbody (red) during cell division. In cells lacking ANKLE1, DNA bridges become elongated and remain unresolved. Using magnetic tweezers, applying tension to DNA induces cleavage by ANKLE1, demonstrating its tension-dependent DNA cutting activity. Image adapted from Jiang et al, Nature Communications (2025).*

An international research team has identified a human protein, ANKLE1, as the first DNA-cutting enzyme (nuclease) in mammals capable of detecting and responding to physical tension in DNA. This 'tension-sensing' mechanism plays a vital role in maintaining genetic integrity during cell division—a process that, when disrupted, can lead to cancer and other serious diseases.

The study, published in *Nature Communications*, represents a major advance in the understanding of cellular DNA protection. The research was conducted through a cross-disciplinary collaboration between Professor Gary Ying Wai CHAN's laboratory at the School of Biological Sciences, The University of Hong Kong (HKU) and Dr Artem EFREMOV's biophysics team at Shenzhen Bay Laboratory (SZBL), with additional contributions from researchers at the Hong Kong University of Science and Technology (HKUST) and the Francis Crick Institute in London.

DNA under stress: the hidden danger during cell division

Every time a cell divides, it must accurately replicate and segregate its DNA. However, this process can sometimes go wrong, leaving DNA entangled and forming 'chromatin bridges'—threads of genetic material that stretch between the two new cells as they try to separate. These bridges break under the mechanical tension generated as cells pull apart, potentially causing severe genetic errors linked to cancer and immune disorders.

'Think of these chromatin bridges as tightropes under tension during cell division,' explains Professor Gary Chan, senior author of the study. 'If they snap suddenly, it can wreak havoc on the genome, causing mutations and instability.' Until now, scientists have not fully understood how cells safely resolve these tense DNA bridges without triggering catastrophic damage.

ANKLE1: the genome's first 'tension-sensing' DNA cutter

The research reveals that ANKLE1, a protein previously associated with DNA repair, functions as a specialised 'tension sensor' nuclease during cell division. Using advanced single-molecule experiments—where individual DNA molecules are manipulated with tiny magnetic tweezers—the team discovered that ANKLE1 can 'feel' when DNA is stretched or twisted. Remarkably, ANKLE1 only cuts DNA under tension or when DNA is supercoiled (twisted), as occurs in overstretched chromatin bridges. This precision prevents the DNA from breaking randomly, which could otherwise cause genetic chaos.

'Our discovery shows that ANKLE1 acts like a smart pair of scissors,' says Dr Artem Efremov, co-senior author and biophysics expert. 'It only cuts DNA when it is really needed—when the DNA is stretched and at risk of breaking in a harmful way. This is a completely new way for cells to sense and respond to mechanical stress on their genetic material.'

The team combined traditional biological techniques with cutting-edge biophysical tools, applying controlled forces to DNA molecules while observing ANKLE1's activity in real time. 'This project could only have succeeded by bringing together expertise from both disciplines,' notes Professor Chan. 'By using physics-based approaches, we could see how ANKLE1 responds to the physical state of DNA, something that is invisible with standard biological methods.'

Implications for genome stability and cancer therapy

This discovery marks a significant step forward in understanding how cells safeguard genetic material under physical stress. By revealing how ANKLE1's role as a tension-sensitive DNA cutter, the research provides crucial insights into how cells prevent dangerous DNA breaks that can lead to cancer and other diseases.

Intriguingly, the study suggests that inhibiting ANKLE1 could push cancer cells—already prone to genome instability—beyond a critical threshold, potentially making them more susceptible to existing treatments. As a result, ANKLE1 may emerge as a novel therapeutic target, offering new strategies to exploit tumour vulnerabilities while deepening the knowledge of genome maintenance.

The full paper, titled 'ANKLE1 processes chromatin bridges by cleaving mechanically stressed DNA' is available at https://www.nature.com/articles/s41467-025-65905-7

For more about Professor Gary Ying Wai Chan's work: https://sites.google.com/site/garychanlab

For more about Dr Artem Efremov's work: https://artemefremovlab.com

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