A new tool to study cell movement promises to advance cancer research

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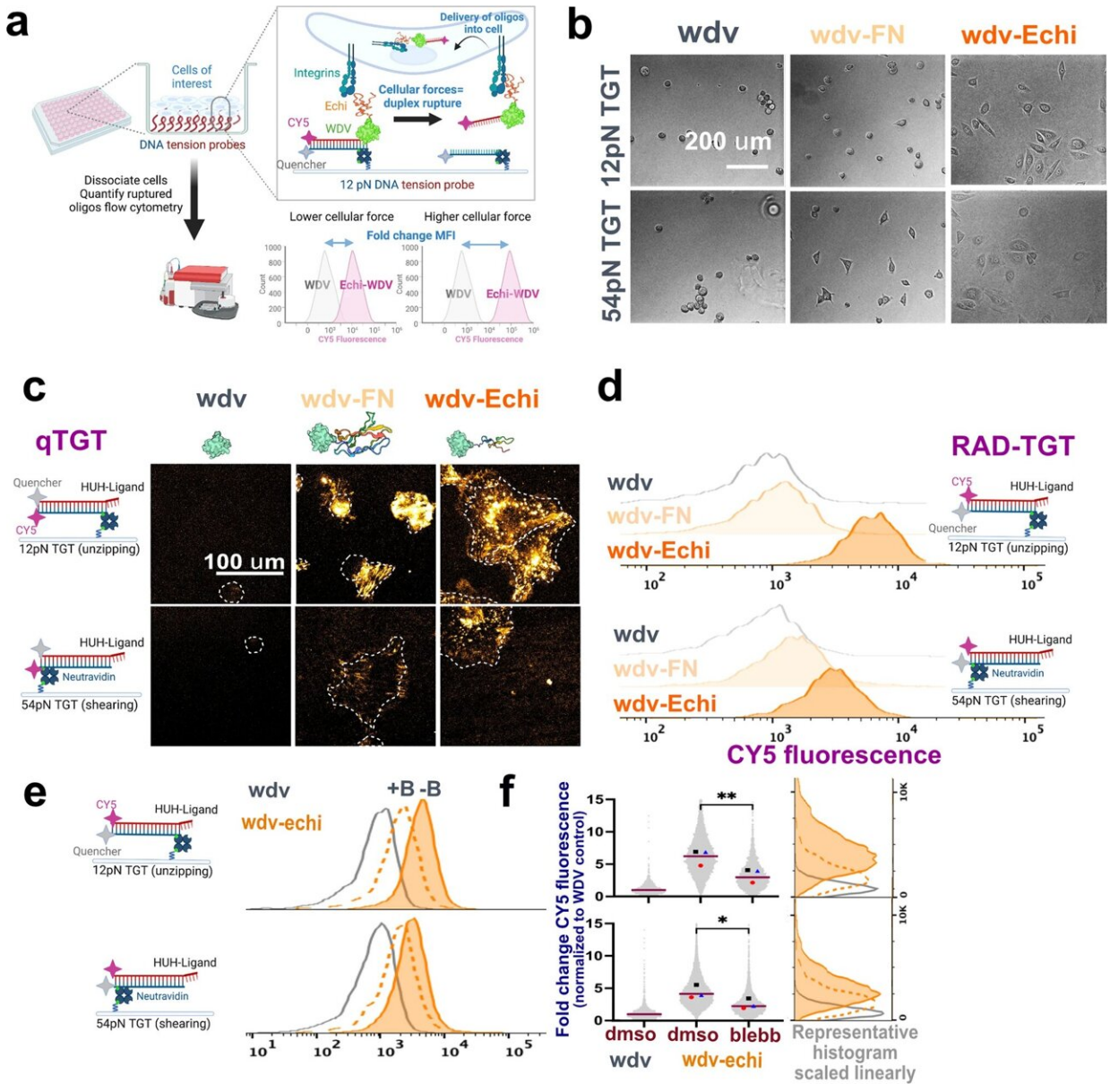

Overview and validation of RAD-TGT function in CHO-K1 cells. **a** Conceptual schematic of the force-induced rupture and readout of RAD-TGTs. **b** Brightfield imaging at 20x of adhesion assay of cells on RAD-TGT surfaces with either WDV, WDV-FN, or WDV-Echi ligand and 12 or 54 pN rupture force. **c** Fluorescent imaging at 40x of qTGT fluorescent duplex rupture of cells plated on TGT surfaces of varying ligand and rupture force composition. White dotted lines denote cell borders. **d** Flow cytometry results of cells plated on RAD-TGT surfaces with different ligand and rupture force composition. **e** Representative histogram showing the effect of para-amino-blebbistatin treatment on TGT rupture. **f** SuperPlots of CY5 fluorescence of each cell from three biological replicates normalized to WDV median fluorescence with symbols for medians of biological replicates. Representative histograms turned 90° and scaled linearly for reference. Gray histograms are WDV only, dotted lines are with para-amino-Blebbistatin, and solid orange is with DMSO treatment as control. $**p = 0.001387$, $*p = 0.015441$. Statistics were performed using one-way ANOVA of the medians of biological replicates. Source data are provided as a Source Data file. All cartoons and schematics were created with Biorender.com. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-38157-6

Some diseases can be diagnosed by identifying physical changes in tissue, such as the hardening of arteries during heart disease. Diseased cells often exhibit different mechanical characteristics, or mechanotypes, than normal cells. Efficient tools for measuring mechanotypes could allow doctors to diagnose diseases at an early stage, predict whether a tumor might metastasize, and identify effective drugs and genes linked to certain diseases.

In a promising development for cancer screening and treatment, groundbreaking research published in *Nature Communications* by a team of U of M researchers from the Medical School and College of Biological Sciences has led to a new laboratory test to measure cell mechanotypes quickly and easily.

Cells constantly move through the body and interact with other cells. Cancer cells may move more aggressively than other cells, in some cases pulling on the tissue around them. Metastatic cancer cells sometimes exhibit less pull than others. In the past 25 years, scientists have evaluated these pulling forces with tools like microscopy, which are effective but difficult to use and time-intensive, resulting in bottlenecks for cancer research.

The research team wanted to develop a more rapid method of evaluation. They discovered:

- By using tension gauge tethers (TGTs), or small bits of double-stranded DNA that break apart when cells attach and pull on them, they were able to evaluate how different types of cancerous cells differentially break apart the DNA.
- By attaching fluorophores to TGTs that get delivered into the cells interacting with the TGTs, they can evaluate thousands of cells quickly without microscopy and also sort cells according to their mechanotype.
- The RAD-TGT ("Rupture and Deliver Tension Gauge Tethers") tool can differentiate between mechanotypes among mixed populations of cells, opening up the possibility of identifying genes linked to diseases.

"We can measure thousands of cells' fluorescence in minutes using an instrument called a flow cytometer and then isolate the cells by their distinct mechanotype," said author Wendy Gordon, associate professor of biochemistry, molecular biology and biophysics. "We are now working to use this assay to study the mechanotypes of several different cancers."

The RAD-TGT tool also helps evaluate problematic cells at different states. For example, in a metastasizing cancer, the cancer cells may

become squishy to squeeze through blood vessels and enter other parts of the body. In that case, a drug that makes cells more firm could be beneficial. This tool will help researchers evaluate the varying states of the disease and cell progression.

More information: Matthew R. Pawlak et al, RAD-TGTs: high-throughput measurement of cellular mechanotype via rupture and delivery of DNA tension probes, *Nature Communications* (2023). DOI: 10.1038/s41467-023-38157-6

Provided by University of Minnesota

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