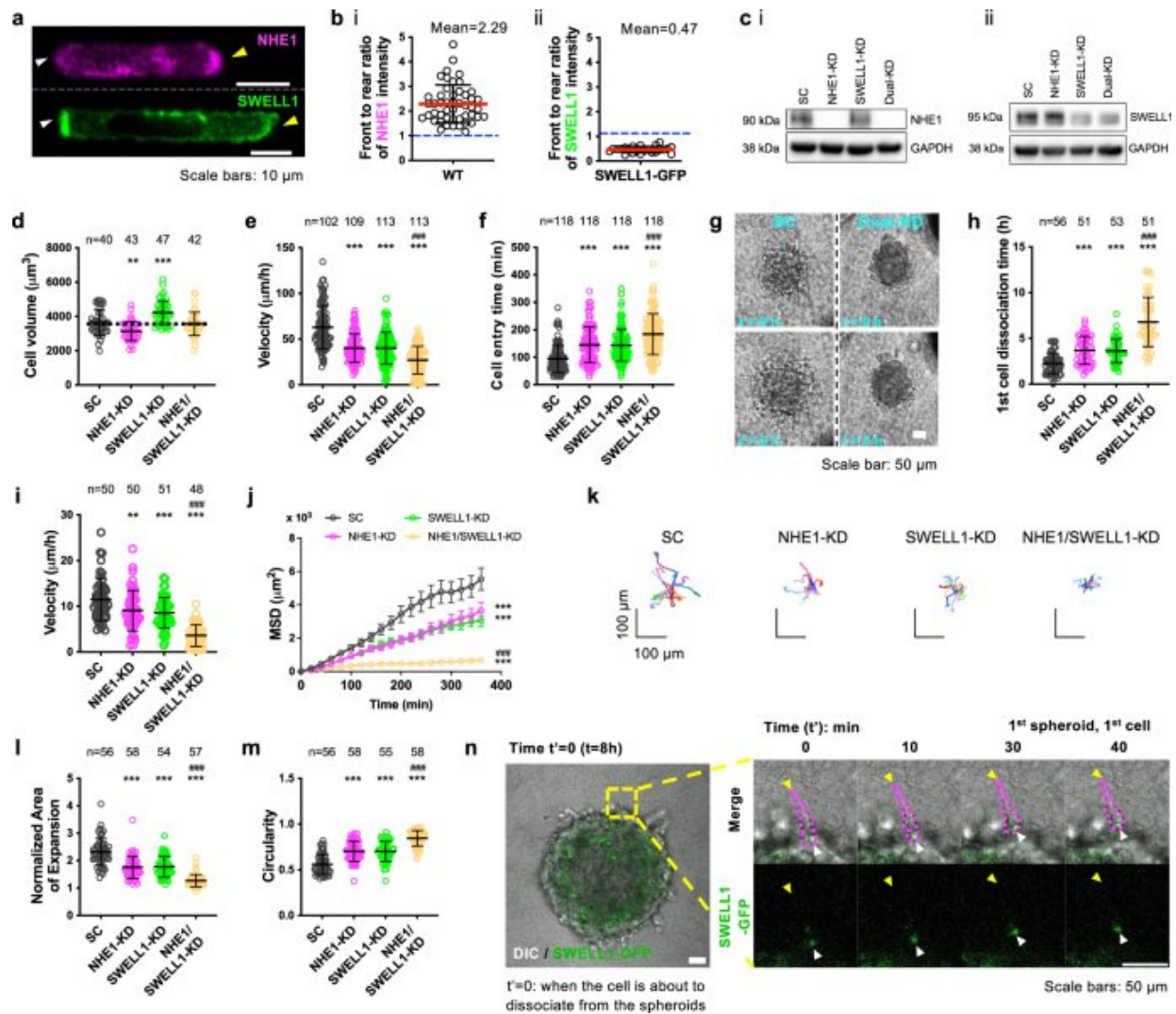


New research explores how cancer cells spread in human body

November 2 2022, by Chris Kocher



Distinct spatial localization patterns of NHE1 and SWELL1, and their roles in cell volume regulation and confined migration. a) Top: Image of a cell stained for NHE1 showing preferential localization at the leading edge (yellow

arrowhead). Bottom: Image of another cell showing intense localization of SWELL1-GFP at the cell rear (white arrowhead). b) Front to rear ratio of (i) endogenous NHE1 (n = 48) or (ii) SWELL1-GFP intensity (n = 23) in confined cells. Data represent mean \pm SD from four independent experiments. c) Western blots of cells transduced with SC or shRNA sequences against NHE1 and/or SWELL1. GAPDH served as a loading control. Uncropped blots in Source Data. d) Effects of NHE1 and/or SWELL1 knockdown on cell volume inside confining channels. Data represent mean \pm SD for cells analyzed from three independent experiments. e, f) Effects of NHE1 and/or SWELL1 knockdown on e migration velocity and f cell entry time in confining channels. Data represent mean \pm SD for cells analyzed from 3 independent experiments. g) Images showing dissemination of SC and dual NHE1- and SWELL1-KD cells from spheroids embedded in 3D collagen gels at t = 0 and 5 h. h–k Effects of NHE1 and/or SWELL1 knockdown on h) the time for the first cell to dissociate from spheroids, and the i) migration velocity, j) mean squared displacement, and k) trajectories of disseminated cells in 3D. Data represent mean \pm SD for cells analyzed from three independent experiments. l, m) Effects of NHE1 and/or SWELL1 knockdown on l normalized area of expansion at t = 12 h relative to t = 0 and m circularity of the spheroids at t = 0 embedded in 3D collagen gels. Data represent mean \pm SD for cells analyzed from three independent experiments. n) Time-lapse montage of a SWELL1-GFP-tagged cell (outlined by dashed magenta lines) dissociating from a spheroid embedded in collagen. White arrowheads denote SWELL1 polarization at the cell rear. Yellow arrowheads indicate the cell leading edge. **p = less than 0.01 and ***p = less than 0.001 relative to SC, ###p = less than 0.001 relative to either of single KD cells. Tests performed: d, e, h, i, m one-way ANOVA followed by Tukey's post hoc test, f, l Kruskal–Wallis followed by Dunn's, or j two-way ANOVA followed by Tukey's. The number of cells analyzed is indicated in each panel. Cell model: MDA-MB-231. Credit: *Nature Communications* (2022). DOI: 10.1038/s41467-022-33683-1

For decades, figuring out exactly why cancerous tumors form in the human body has been a goal for scientists, but knowing how cancer cells spread is also key to fighting the often-deadly disease.

The osmotic engine model of cancer motility has shown that confined cells move by taking in water at the leading edge and expelling it from the back, causing propulsion. However, the exact molecules that regulate those cells' rear shrinkage have remained elusive.

New research published in *Nature Communications* answers that question about cell locomotion, offering a few more steps along the path to future cancer treatment. Assistant Professor Yizeng Li, who joined the Biomedical Engineering Department at Binghamton University's Thomas J. Watson College of Engineering and Applied Science this fall, co-authored the paper along with collaborators from Johns Hopkins University, the University of Maryland, the University of Alberta and the Universitat Pompeu Fabra in Spain.

Researchers experimented with breast cancer cells in a three-dimensional matrix to study their behavior. As previously confirmed, a molecule called sodium/proton exchanger 1 (NHE1) causes water to be absorbed—but the researchers also discovered that another [protein](#) at the back, called SWELL1, polarizes the [cell membrane](#) in a way that leads to movement.

"We clearly show that NHE1 concentrated at the front is responsible for intake of water," Li said. "At the back of the cell, SWELL1 will remove chloride—and by removing chloride, it also will remove water. We completed the story about how water goes in and how it leaves."

Li received her Ph.D. from the Department of Mechanical Engineering at the University of Michigan-Ann Arbor, and she was a postdoctoral researcher at Johns Hopkins University's Department of Mechanical Engineering and Institute for NanoBioTechnology. Her background is in theoretical mechanics and applied mathematics with applications to biophysics and mechanobiology.

"Mechanobiology is at the interface of cell biology, physics and mechanics. Most of my work has been concentrated on cell migration, cell volume control and those related questions," she said.

"I developed the mathematical model for this work. To better understand the biophysical mechanisms behind cancer cell motility, I developed a physiology-based model, instead of a phenomenon-based model. The model combines fluid dynamics, cytoskeleton structure and microscopic details such as ionic transportation. The model prediction very much matches the experimental data."

With about 40% of the U.S. population diagnosed with cancer at some point in their lifetimes, research like that from Li and her colleagues could have wide implications for slowing down or halting the deadly disease—even if treatments are years down the road.

"We want to understand under what conditions [tumor](#) cells may migrate and under what conditions we can prevent it," she said.

More information: Yuqi Zhang et al, Polarized NHE1 and SWELL1 regulate migration direction, efficiency and metastasis, *Nature Communications* (2022). [DOI: 10.1038/s41467-022-33683-1](https://doi.org/10.1038/s41467-022-33683-1)

Provided by Binghamton University

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