Bioengineers explore how tumor mechanics and tiny messengers could shape the future of cancer research

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Seung-Hyun (Bri) Ko, Ph.D. student co-advised by Jina Ko and Ravi Radhakrishnan, aliquoting isolated extracellular vesicles (EVs) from a triple-negative breast cancer cell line. Credit: Penn Engineering

When Ph.D. student Kshitiz Parihar began combing through dozens of research papers on two seemingly different topics—tumor mechanics and extracellular vesicles, tiny packages of proteins and genetic material secreted by cells—he noticed something surprising: the two fields were speaking to each other.

Together with his advisor, Ravi Radhakrishnan, Professor of Bioengineering and Chemical Biomolecular Engineering and Herman P. Schwan Department Chair of Bioengineering, Parihar co-authored a literature review, published in *Nature Biomedical Engineering*, that highlights these hidden connections.

But for the pair, the review is less about summing up the state of the science and more about charting where the field of mechanobiology, the study of how physical forces like stiffness and pressure affect how cells grow, move and communicate, is headed and how the Radhakrishnan Lab at Penn Engineering is uniquely positioned to drive it forward.

Reviewing past research to inform the future

Reviews, Radhakrishnan explains, aren't just summaries. They provide the scaffolding that ties disparate studies together, helping researchers and students new to the field see a bigger picture.

"In cancer research, we know a lot about how cells send chemical signals," he says. "But when we put together the literature on mechanics and vesicles, we started to see cancer in a new way, not just as altered signaling, but also as a problem of trafficking and transport."

For Parihar, writing the review was a chance to learn by connecting dots across fields.

"It was fascinating to see that tumor mechanics and extracellular vesicles

may not be as different as they seem," he says. "When you put them together, you realize they're shaping the same story of cancer progression."

Tiny vesicles, big questions

Over the past decade, extracellular vesicles, or EVs, have drawn attention for their role as messengers: they carry cargo like proteins and RNA between cells, influencing how tumors grow, how the immune system responds and even how cancers spread to other parts of the body. What makes them so powerful as a research tool is their accessibility.

"Instead of trying to take a biopsy of a tumor, which is difficult and invasive, we can take a simple blood draw and find these vesicles," says Radhakrishnan.

"They're like fingerprints of the cancer cells that released them, and they hold a lot of data that we can leverage for immunotherapy, fundamental cancer research and the basics of mechanics in cancer progression."

But before the data from EVs can truly be helpful in real-world applications, there are still questions to be answered: Why do cancer cells secrete so many more vesicles than healthy cells? And how do those vesicles alter the mechanics of the tissues around them?

Mechanics meets messaging

One of the review's key insights is that mechanics and messaging go hand in hand. Tumors are not just chemically abnormal, they're physically different: stiffer, lumpier, under unique stresses. Those mechanical changes affect how many vesicles cancer cells release and even what cargo the vesicles carry.

Or at least, that's what the researchers hypothesize: both that the surrounding tissue environment affects the vesicles and that the process is reciprocal.

"We're seeing that vesicles don't just respond to the environment," Radhakrishnan says. "They actively reshape it. They can stiffen tissue and prime it for metastasis."

That interplay between mechanics and vesicle biology is opening new avenues for therapies. For example, because vesicles are naturally made by the body, they might be used as more biologically viable drug delivery vehicles, potentially capable of crossing barriers like the blood-brain barrier that synthetic nanoparticles often can't. Combining vesicles with engineered lipid nanoparticles could yield hybrid systems for immunotherapy and cancer treatment.

"Since synthesizing the studies in this review, we have been in collaboration with Jina Ko's lab at Penn Engineering and the Perelman School of Medicine to start to examine how EVs and lipid nanoparticles might work together as a combination drug delivery system that could treat head and neck cancers, particularly oral cancers."

Ravi Radhakrishnan (left) and Kshitiz Parihar (right) stand in front of a schematic of a cell secreting extracellular vesicles and the chemical cargo they carry. Credit: Penn Engineering

Modeling the unobservable

One challenge is that vesicles are so small, they can't be reliably tracked under a microscope. That's where engineering tools come in. Parihar is developing computational models to simulate vesicle movement and interactions, validating those models against experimental data when possible.

"These models are our best way of 'seeing' how vesicles traffic through the body and interact with recipient cells," he explains. "They let us ask

questions about cancer spread and immune communication that we otherwise couldn't. One day, super-resolution microscopy technology will be able to tell us more about how EVs interact with cells, but for now, we turn to advanced computational modeling to answer this question."

Mentoring the next generation

For Radhakrishnan, the review is also about training. His lab thrives at the intersection of biology, engineering, computation and medicine, bringing together collaborators from across Penn.

"These are not problems you can solve from a single perspective," he says. "The students and researchers in my lab work with biologists, engineers and clinicians every day. They're being trained to think bigger than any one discipline."

That philosophy carries into the classroom as well. In the course, BE 5400: Principles of Molecular and Cellular Bioengineering, Radhakrishnan uses case studies and literature reviews to help undergraduate students link theory with real-world problems.

"Often, students ask questions I hadn't considered," he says. "Those questions spark entirely new directions for research."

Parihar adds that one of the most important lessons for young scientists is to stay open.

"Don't treat any one study or paper as the absolute truth," he says. "Look for connections across fields, attend conferences outside your discipline and be willing to imagine the unexpected."

Future mechanobiology research at Penn

The lab's focus on interplay between vesicles and mechanics grew out of a hypothesis developed at Penn by co-author Wei Guo, Hirsch Family President's Distinguished Professor at the School of Arts & Sciences, and collaborators years ago: that cancer progression may be as much about how things move in the cell as it is about chemical signaling alone.

That idea has since gained traction, reshaping how researchers approach the disease.

Now, with new tools, new collaborations and a new generation of scientists, Radhakrishnan and his team are working to turn those insights into therapies.

"Mechanobiology is changing how we think about cancer," he says. "It's not just chemistry, it's physics, it's engineering, it's transport. And Penn is the place where those perspectives and world-class experts come together to solve problems in an interdisciplinary approach.".

More information: Kshitiz Parihar et al, Mechanical regulation of extracellular vesicle activity during tumour progression, *Nature Biomedical Engineering* (2025). DOI: 10.1038/s41551-025-01446-0

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