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Researchers say they've unlocked key to cancer metastasis and how to slow it

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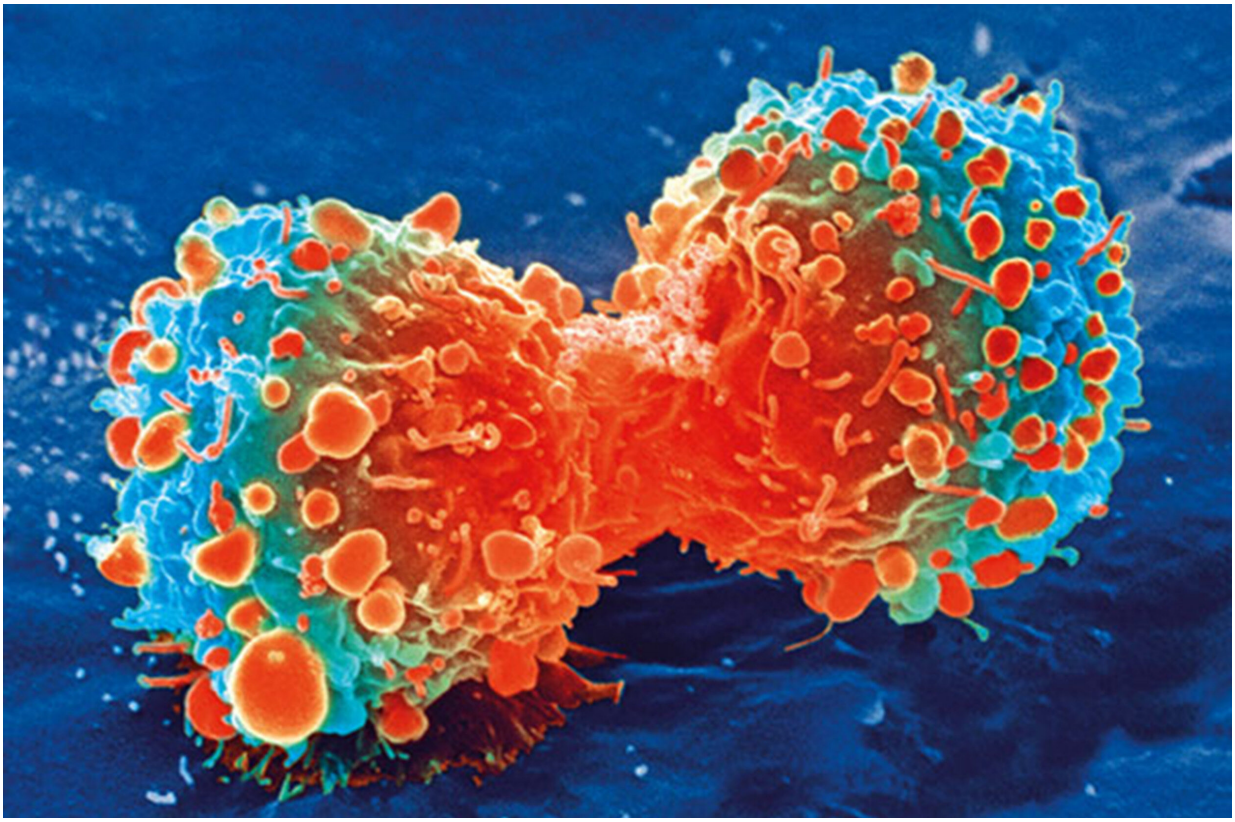

Cancer cell during cell division. Credit: National Institutes of Health

Hasini Jayatilaka was a sophomore at the Johns Hopkins University working in a lab studying cancer cells when she noticed that when the cells become too densely packed, some would break off and start

spreading.

She wasn't sure what to make of it, until she attended an academic conference and heard a speaker talking about bacterial cells behaving the same way. Yet when she went through the academic literature to see if anyone had written about similar behavior in cancer cells, she found nothing.

Seven years later, the theory Jayatilaka developed early in college is now a bona fide discovery that offers significant promise for cancer treatment.

Jayatilaka and a team at Johns Hopkins discovered the biochemical mechanism that tells cancer cells to break off from the primary tumor and spread throughout the body, a process called metastasis. Some 90 percent of cancer deaths are caused when cancer metastasizes. The team also found that two existing, FDA-approved drugs can slow metastasis significantly.

"A female patient with breast cancer doesn't succumb to the disease just because she has a mass on her breast; she succumbs to the disease because (when) it spreads either to the lungs, the liver, the brain, it becomes untreatable," said Jayatilaka, who earned her doctorate in chemical and biomolecular engineering this spring in addition to her earlier undergraduate degree at Hopkins.

"There are really no therapeutics out there right now that directly target the spread of cancer. So what we came up with through our studies was this drug cocktail that could potentially inhibit the spread of cancer."

The study was published online May 26 in the journal *Nature Communications*. The next step for the team is to test the effectiveness of the drugs in human subjects.

Typically, cancer research and treatment has focused on shrinking the primary tumor through chemotherapy or other methods. But, the team said, by attacking the deadly process of metastasis, more patients could survive.

"It's not this primary tumor that's going to kill you typically," said Denis Wirtz, Johns Hopkins' vice provost for research and director of its Physical Sciences-Oncology Center, who was a senior author on the paper.

Jayatilaka began by studying how cancer cells behave and communicate with each other, using a three-dimensional model that mimics human tissue rather than looking at them in a petri dish. Many researchers believe metastasis happens after the primary tumor reaches a certain size, but Jayatilaka found it was the tumor's density that determined when it would metastasize.

"If you look at the human population, once we become too dense in an area, we move out to the suburbs or wherever, and we decide to set up shop there," Jayatilaka said. "I think the cancer cells are doing the same thing."

When the tumor reaches a certain density, the study found, it releases two proteins called Interleukin 6 and Interleukin 8, signaling to cancer cells that things had grown too crowded and it was time to break off and head into other parts of the body.

Previously, Wirtz said, the act of a tumor growing and the act of cancer cells spreading were thought to be very separate activities, because that's how it appeared by studying cancer cells in a petri dish, rather than the 3-D model the Hopkins team used. Many researchers study only cancer cell growth or its spread, and don't communicate with each other often, he said.

Once the cancer cells start to sense the presence of too many other cancer cells around them, they start secreting the Interleukin proteins, Wirtz said. If those proteins are added to a tumor that hasn't yet metastasized, that process would begin, he said.

The team then tested two drugs known to work on the Interleukin receptors to see if they would block or slow metastasis in mice. They found that using the two drugs together would block the signals from the Interleukin proteins that told the cancer cells to break off and spread, slowing - though not completely stopping - metastasis.

The drugs the team used were Tocilizumab, a rheumatoid arthritis treatment, and Reparixin, which is being evaluated for cancer treatment.

The drugs bind to the Interleukin receptors and block their signals, slowing metastasis.

Though metastasis was not completely stopped, Jayatilaka said, the mice given the drug cocktail fared well and survived through the experiment. She said adding another, yet-to-be-determined drug or tweaking the dose might stop metastasis entirely.

Contrary to the hair loss, nausea and other negative side effects patients undergoing chemotherapy suffer, Wirtz said the side effects from the drugs used in the study would be minimal.

Anirban Maitra, co-director of a pancreatic cancer research center at the MD Anderson Cancer Center at the University of Texas, cautioned that clinical trials in humans are needed to prove the theory.

"There's a risk that something that looks so great in an animal model won't pan out in a human," he said.

But Maitra said the study looked promising, in particular because the researchers had used drugs already on the market. It can take a decade to identify a drug that would perform similarly and get it approved, and many similar observations don't advance because of the time and expense it can take to get drug approval, he said.

Muhammad Zaman, a professor and cancer expert at Boston University, called the Hopkins discovery "exciting."

"This paper gives you a very specific target to design drugs against," he said. "That's really quite spectacular from the point of view of drug design and creating therapies."

Zaman said it was important for cancer researchers to use engineering to better understand cancer, as the Hopkins team did.

"This really brings cancer and engineering together in a very unique way, and it really takes an approach that is quantitative and rigorous," he said. "We have to think of cancer as a complex system, not just a disease."

Wirtz predicted a future where cancer would be fought with a mix of chemotherapy to shrink the primary tumor and drug cocktails like the one the Hopkins team developed to ensure it would not metastasize. He compared such a treatment to how HIV/AIDS is treated today.

"We're not going to cure cancer with one therapy or even two therapies; it's going to be drug cocktails," Wirtz said. "That's what saved the day with HIV/AIDS."

Immunotherapy, which uses the body's immune system to fight cancer, also could play a role in a combined method, Wirtz added.

"We're, in research, sometimes incentivized to look at one pathway at a

time, one type of cancer at a time," Wirtz said. "I think oncology has started realizing we're going to need more than one approach."