Stories of Discovery: Can A Common Vitamin Put the Brakes on Breast Cancer?

The Bad Actors Chemotherapy Leaves Behind

The goal of anti-cancer therapy is to kill cancer cells and destroy the tumor. Although research has led to many new and promising drugs, even these innovative treatments can fail to kill every tumor cell. Tumor cells that survive the anti-cancer drugs can live undetected in the body for many years. For reasons doctors don't yet understand, these hidden tumor cells can become active again and form new tumors at distant sites, a process known as metastasis. Metastatic breast cancers are usually very aggressive and treatments are limited. But what if we knew how to keep these persistent cancer cells quiet or make them less aggressive? Could we prevent or reduce metastasis? Dr. Antonio F. Santidrian, a Komen-funded postdoctoral fellow at the Scripps Research Institute in La Jolla, CA, and his research mentor Dr. Brunie Felding-Habermann, believe they have found a way by using different forms of Vitamin B3 (nicotinamide and nicotinic acid.)

Finding the Switch

Finding a way to keep lurking cancer cells quiet begins with understanding what kind of switch turns on these non-aggressive tumor cells. This has become a focus of Dr. Felding-Habermann's research at the Scripps Research Institute where she and her lab have been studying how breast cancer spreads for nearly twenty years.

"Through working with breast cancer advocates and people in the clinic, we have one really strong focus in mind and that is to generate information that will help patients get better," says Dr. Felding Habermann. "We are committed to taking on the challenges that are being brought to us by the advocates, and want to see the field (of breast cancer research) move away from baby-step advances to breakthrough-types of discoveries."

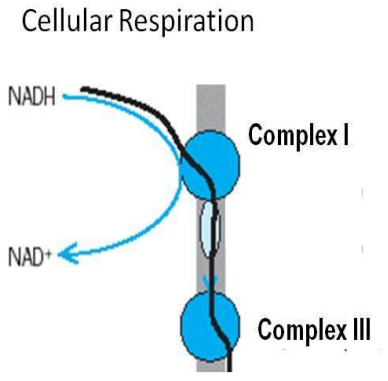
In the course of her research, Dr. Felding-Habermann's laboratory has discovered that some breast cancer cells that metastasize to the brain have different levels of several proteins, called enzymes, compared to cells that do not metastasize. These enzymes control the metabolism, or energy processes, of the cell.

Following a hunch, Dr. Antonio F. Santidrian, a Senior Research Associate in Felding-Habermann's lab and Komen Fellow, decided to study how the differences in metabolism were affecting the behavior of the metastatic breast cancer cells. His focus was on a particular protein complex, called Complex I, because it is defective in the highly aggressive breast cancer cells.

How It Works

Complex I is a key component of cellular respiration, the process in which the cell consumes oxygen and produces energy. A major function of Complex I is to generate NAD^+, a molecule that is essential for many important processes in a healthy cell. Dr. Santidrian found that the production of NAD^+ is disturbed in the aggressive breast cancer cells.

As illustrated here, cellular respiration begins as NADH transfers its energy to Complex I and is converted to NAD+. In healthy cells, there is a balance of NADH and NAD+ levels. In cells with abnormal Complex I function, an excess of NADH accumulates. This causes the tumor cells to panic and activate survival pathways that promote tumor growth.



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Let Sleeping Cancer Cells Lie

Santidrian suspected that an imbalance of NAD^+ and NADH was responsible for the aggressive behavior in the cancer cells that metastasized. To test this hypothesis, he cleverly transferred a Complex I gene found in yeast to the human breast cancer cells in an attempt boost Complex I activity. He then transplanted the modified cancer cells into mice to see if they would grow and metastasize. He found that the breast cancer cells, which did not have the newly added yeast gene, grew rapidly and metastasized in the mice, while cells that had the working yeast gene did not.

Convinced that the excess NADH was making the tumor cells more aggressive, Santidrian tried a simpler approach. Because NAD^+ is made by the cell from vitamin B3, he added a form of vitamin B3 called nicotinamide to the drinking water of the mice. He found that the nicotinamide-supplemented water was able to reduce tumor growth and prevent metastasis, even in the most aggressive breast tumors.

"This is the first study to show a direct relationship between abnormal Complex I and tumor cell aggressiveness," noted Dr. Felding-Habermann. "It represents the kind of breakthrough discovery we hope to achieve."

What's Next?

Because the vitamin B3 compound, a building block of NAD^+, appears to keep cancer cells from growing, it could be used as a non-toxic addition to standard chemotherapy. To test this idea, Dr. Santidrian is now studying the effects of combining the vitamin B3 compound with chemo- and radiation therapy in breast cancer mouse models. If results are promising, the next step will be to study this approach in a clinical trial in humans. Because vitamin B3 compounds are well known, the path to a clinical trial won't require years of development or be delayed by regulatory requirements, which have already been satisfied. That means that these studies could potentially have a clinical impact in a relatively short term.

What does it mean for breast cancer patients?

Metastasis is the leading cause of breast cancer-related deaths. Dr. Santidrian's findings could be an important step forward in reducing, and even preventing, metastasis from ever occurring. Even more, because vitamin B3 compounds are non-toxic and act to suppress breast cancer progression, they could be very effective in preventing metastasis after successful cancer therapy.

"It will be important to analyze if vitamin B3 compounds can prevent metastasis and prolong cancer free survival after successful breast cancer treatment," notes Dr. Felding-Habermann. *"The goal is not to replace the standard of care,"* she adds, *"but rather to complement existing therapies to prevent recurrence, reduce mortality, and achieve better outcomes."*

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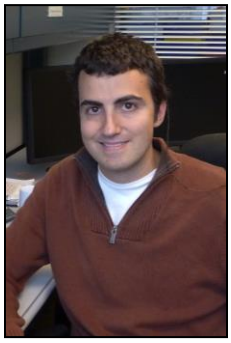
The Faces Behind the Science



Dr. Antonio F. Santidrian received his Ph.D. from the University of Barcelona, Spain in 2007 and joined the Felding-Habermann lab in 2008. His primary research interest is in tumor cell metabolism, the study of how tumor cells regulate their energy to grow and survive. He was drawn to Dr. Felding-Habermann's laboratory not only by her work in breast cancer metastasis, but also by her compassion for the breast cancer patient and his personal conviction to want to make a difference.

"In Barcelona, there isn't a breast cancer advocate community like we have here," he said. *"Meeting the people whom I am trying to help has changed how I view the work I'm doing. There's a real urgency for new discoveries that will change the breast cancer experience."*

While his Komen fellowship will be ending this summer, Santidrian's work on breast tumor metabolism will not end there. His goals are to build on his fellowship experience and develop an independent career in breast cancer research to further understand how tumor metabolism affects cancer progression.

Dr. Brunie Felding-Habermann has dedicated her career to the study of breast cancer metastasis. She feels a personal commitment to respond to the compelling challenges presented by the breast cancer advocates and clinical communities, and to instill a sense of urgency in the young members of her lab. Her interaction with breast cancer advocates has influenced all projects in her lab; so, patients' needs for more effective treatments that can prevent or stop cancer's spread remains her primary focus.

Dr. Felding-Habermann credits Dr. Santidrian for the contributions he's made to her laboratory through his independent investigation, which has lead to exciting new collaborations and plans for future projects, including a clinical trial.

"Antonio's study has motivated our lab to focus even more on metabolic alterations in breast cancer progression and has thereby influenced just about every project we're pursuing in breast cancer metastasis. None of this would have been possible without Komen's support. "

The findings of these studies have been published in the March 2013 issue of the Journal of Clinical Investigation.