

Team finds potential cause for deadly breast cancer relapse

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Researchers at the UNC School of Medicine, working with cell lines in a lab, have discovered why some of the most aggressive and fatal breast cancer cells are resistant to chemotherapy, and UNC scientists are developing ways to overcome such resistance.

Adriana S. Beltran, PhD, a research assistant professor in the department of pharmacology, found that the protein Engrailed 1 is overexpressed in basal-like carcinomas and designed a chain of [amino acids](#) to shut down the protein and kill basal-like tumors in the lab.

"Patients with basal-like [breast cancer](#) tend to initially respond well to chemotherapy, but it's common for patients to relapse even more aggressively," said Beltran, the first author of a paper published in the journal *Oncogene*. "We believe that relapse is caused by a small number of cancer cells that have stem cell properties that allow them to survive chemotherapy. In these cells we've identified the overexpression of Engrailed 1."

Beltran and her colleagues – UNC pharmacologist Lee Graves, PhD, and former UNC pharmacologist Pilar Blancafort, PhD – discovered that Engrailed 1 is not involved in the rapid proliferation of cells that cause tumor growth. Nor is Engrailed 1 present in luminal tumors – the most common form of breast cancer. The culprit protein only appears in basal-like breast cancer.

In fact, Engrailed 1 is normally confined to the brain, where it protects

neurons from cell death and helps maintain their normal activity. The absence of the protein in the brain has been linked to the onset of Parkinson's disease. But there is no known function of Engrailed 1 within [breast tissue](#).

"We think that Engrailed 1 confers protective features to breast [cancer cells](#), similar to the features observed in long-lived neurons," Beltran said. "This may explain why these cells survive and become resistant to chemotherapy in our experiments."

The researchers found Engrailed 1 through a series of experiments designed to find genes highly expressed in basal-like cells but not in luminal breast cancers. They discovered that Engrailed 1 was most highly expressed in cell lines isolated from [inflammatory breast cancer](#).

Working with the UNC Michael Hooker Proteomics Center, Beltran and colleagues also determined that Engrailed 1 was associated with the gene EPRS, which expresses an enzyme that controls messenger RNA and protein synthesis, particularly in proteins involved with inflammation.

"Inflammation is associated with cancer development," Beltran said. "It's interesting to us that Engrailed 1, alone, is able to control inflammatory responses that may promote more aggressive forms of cancer."

Why Engrailed 1 is manifested in cancerous breast tissue remains a mystery. "Nature seems to always find a way," Beltran said. "Cancer cells are part of nature; everything in nature strives to survive."

But Beltran and her colleagues might have found a way to stop Engrailed 1. After studying how Engrailed 1 binds to DNA and other proteins, the researchers created a synthetic peptide – a chain of amino acids – that can stifle the binding power of Engrailed 1. In [cell lines](#) – not in animals or patients – Beltran and colleagues used their peptide to disrupt Engrailed 1 from binding to its protein partners and DNA.

"Cancer cells need Engrailed 1 to live," Beltran said. "The peptide abolishes all interactions of Engrailed 1, and as a consequence Engrailed 1 cannot perform its functions, causing rapid cell death of the cancer cell."

"The goal now is to validate our findings in animal models."

If Engrailed 1 turns out to be as critical to basal-like metastasis as it seems from this basic research, then a drug could be developed to fight cancer relapse in some of most deadly forms of breast cancer.

More information: www.nature.com/onc/journal/vaol/nc2013422a.html

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