# Study sheds light on why some breast cancers have limited response to immunotherapy

August 21 2017

Jonathan Serody, M.D., UNC Lineberger member and the Elizabeth Thomas Professor in the UNC School of Medicine, is first author of a study that investigated why drugs that are designed to unleash the immune system against cancer were ineffective in a type of triple negative breast cancer with a heavy presence of immune cells. Credit: Brian Strickland/UNC Lineberger

UNC Lineberger Comprehensive Cancer Center researchers have identified a possible reason why some aggressive breast cancers are unresponsive to certain immunotherapy treatments, as well as a potential solution.

In the *Journal of Clinical Investigation*, researchers report on their study that explored a perplexing question: Why were drugs designed to unleash the immune system against cancer ineffective in a type of triple negative breast cancer with a heavy presence of immune cells? Their findings could lead to a strategy to improve immunotherapy responses in the "claudin-low" subtype of breast cancer.

"We were trying to figure out why a tumor made up, in some instances, of half immune cells doesn't respond to a treatment that should ramp up immune cells present in the tumor," said the study's senior author Jonathan Serody, MD, UNC Lineberger member and the Elizabeth Thomas Professor in the UNC School of Medicine. "I think it's important for us to try to start segregating out the types of tumors that don't respond to these treatments at a much granular genomic level, and try to figure out new mechanisms to enhance the response rate to immunotherapy."

The American Cancer Society estimates that approximately 12 percent of breast cancers are "triple negative," meaning they lack three cell surface receptors that are known to help drive the cancer. Triple negative breast cancer tumors typically grow faster and come back sooner than other breast cancer types. There are no targeted treatments for these cancers.

In a subset of triple negative breast cancers known as "claudin low," researchers found an elevated level of immune cells in and around the tumors. They believed this would help the body fight the cancer. However, the researchers found the opposite: "Checkpoint inhibitors," a

type of immunotherapy that works by unlocking the immune system's brakes against cancer, were ineffective in this subtype.

They determined with gene expression analysis that, instead of being flooded with immune cells that attack cancer tumors, claudin-low tumors had a high concentration of regulatory T-cells - a type of immune cell that suppresses the body's defenses. Claudin-low tumors were releasing a chemical signal to attract these regulatory T-cells.

"This regulatory T-cell population is preventing the immune system from rejecting the cancer," said UNC Lineberger's Benjamin Vincent, MD, an assistant professor in the UNC School of Medicine. "We thought if we could get rid of those cells, we could help the immune system better fight the breast cancer cells."

In an effort to allow the immune-stimulating cancer treatments to work, the researchers tested an investigational approach to deplete the regulatory T-cells, and they combined the treatment with a checkpoint inhibitor in order to try to improve outcomes. This combination slowed tumor growth. They believe they have identified a key aspect of what is preventing immunotherapy treatments from working.

"This finding may shed some light on why response rates to immunotherapy treatments remain low in triple negative breast cancer," Vincent said. "We are looking to understand why patients who don't respond don't respond, and what we can do to render their tumors immunotherapy responsive."

Vincent is helping to lead a clinical trial testing this strategy to improve responses to checkpoint inhibitors. Researchers also believe these findings may also underscore the need to study other cancer types at a genomic level to understand differences in response rates to immunotherapy treatments.

"This speaks to the mission of UNC Lineberger, which is to conduct groundbreaking basic science research, but always with the mission of extending and improving the lives of patients as our end goal," Vincent said.

**More information:** Nicholas A. Taylor et al, Treg depletion potentiates checkpoint inhibition in claudin-low breast cancer, *Journal of Clinical Investigation* (2017). DOI: 10.1172/JCI90499

Provided by UNC Lineberger Comprehensive Cancer Center