Yajaira Suarez, PhD

Attacking Cancer Cells from the Outside

Most cancer treatments are a direct assault on cancer cells through radiation, chemotherapy, or targeted therapy. Yet, new alternative approaches are also showing tremendous promise. "Targeting cancer cells is important," said Yajaira Suarez, PhD, Deputy Chair and Anthony N. Brady Associate Professor of Comparative Medicine, "but we are interested in the other side."

Dr. Suarez is referring to the ecosystem surrounding the cancer cells, the 'tumor microenvironment.' She studies how that environment influences the tumor growth. More specifically she is interested in two types of cells within the tumor microenvironment: endothelial cells, which create blood vessels, and macrophages, white blood cells integral to the immune system. Her research focuses on the novel mechanisms that regulate the functions of these two cell types.

When normal cells become cancerous and start to proliferate, she explains, they secrete factors whose signals cause two responses. One signal stimulates endothelial cells to produce blood vessels to feed and oxygenate the tumor. Another signal tells the immune system to send white blood cells to fight the mutating cancer cells. "But because these macrophages are in the microenvironment, with factors secreted by the tumor," explained Dr. Suarez, "they become addicted, let us say, and transform from their normal function. Instead, they start helping the tumor to grow."

To understand the mechanisms behind these two actions, Dr. Suarez and her colleagues turned their attention to microRNAs within the tumor microenvironment. MicroRNAs are small noncoding fragments of RNA that don't produce protein. That makes them sound like molecular nonentities, but the reality is far different.

"They interact with RNAs that produce proteins," said Dr. Suarez, "and they regulate gene expression. That leads to controlling the level of these proteins and therefore controlling cell function. And these microRNAs can control not just one RNA molecule, but different RNA molecules, so they control different proteins."

More importantly, she adds, the RNAs targeted by microRNAs are not random, but are selected to command signaling pathways and metabolic pathways. "This is the beauty of microRNAs," she said. "Because they control different pathways and different proteins, they give you this ability to target more than one protein in antitumor treatments, so you can get an overall effect that is more pronounced."

Dr. Suarez and her colleagues knew that the most upregulated microRNA in solid tumors is microRNA-21 (miR-21). It is also overexpressed in cells from the tumor microenvironment. Dr. Suarez's team used animal models to analyze the links between miR-21, the tumor microenvironment, and growth. They found that miR-21 sends signals from the tumor microenvironment that regulate cells associated with tumorigenesis, including endothelial cells and tumor-associated macrophages (TAMs).

Next, using a mouse model, they removed miR-21 from the macrophages to see what would happen. "Everything changed," said Dr. Suarez. In the paper reporting their results, published in the *Journal of Clinical Investigation*, the scientists wrote that the absence of miR-21in the macrophages "caused a global rewiring of their transcriptional regulatory network." The macrophages shook off their addiction and started instructing T cells to kill cancer cells, shrinking the tumor. To a similar effect, the endothelial cells stopped forming blood vessels that fed the tumor.

"By targeting miR-21 in the macrophages, we were able to reduce tumor growth through two different mechanisms," explained Dr. Suarez. These findings suggest clear benefits of targeting not only the cancer cells but its surrounding microenvironment. When signals from the microenvironment don't reach the tumor, the power of the cancer treatment gets amplified because the T cells strengthen as the tumor's vasculature withers.

Dr. Suarez calls the paper a proof-of-concept that points the way to other possible uses of this strategy. For instance, tumors often develop resistance to immunotherapies. Combining such therapies with a drug that targets microRNAs in the tumor microenvironment could unleash fresh hordes of T cells that boost the immune effect. A common side effect of radiation therapy, continues Dr. Suarez, is masses of macrophages, which can overwhelm the radiotherapy. That might be reversed by targeting miR-21 in the macrophages.

Dr. Suarez and her colleagues are now testing all these possibilities. She believes that other microRNAs could be targetable as well, not only in macrophages and endothelial cells, but in other cells within the tumor microenvironment.

She emphasizes that her research emerges from her collaborations at Yale. "The Yale environment is fantastic," said Dr. Suarez. "The investigators, the teams, the meetings with people in the Cancer Center about signaling—everything is set up to produce more insight and better ideas to do better research."