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 tumor sides.”

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 reproduce, the RNAs they emit interact with factors whose signals cause two responses. One signal stimulates endothelial cells to produce blood vessels to feed and oxygenate the tumor. “But because these vessels can grow uncontrollable, we call it ‘tumor vasculature withers,’” explained Dr. Suarez, “and they regulate gene expression. That leads to a side effect of radiation therapy, continues Dr. Suarez, is masses that don’t get better, masses that grow back.”

Another signal tells the immune system to send white blood cells to kill the mutating cancer cells. “But because these macrophages are ‘addicted,’ let us say, and transform from their normal function, they become nonentities, but the reality is far different,” said Dr. Suarez. “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.”

“Yet, importantly,” she adds, “the RNAs targeted by microRNAs are not random, but are selected to control 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 specifically than one protein in a tumor microenvironment, 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 signals from the tumor microenvironment that regulate cells associated with tumor microenvironment, including endothelial cells and tumor-associated macrophages (TAMs).

Next, using animal models, 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-21 in the macrophages ‘caused a global rewiring of their transcriptional regulatory network.’ They found the macrophages stopped instructing the immune system to send 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. Those 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 goes amplified because the T cells stop strengthening the tumor’s vasculature withers.”

Dr. Suarez calls the paper a proof-of-concept that points to the way 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 break the resistance to immunotherapies.”

When signals from the tumor microenvironment that regulate cells associated with tumor microenvironment, including endothelial cells and tumor-associated macrophages (TAMs), gets amplified because the T cells strengthen as the tumor’s mass increases, the macrophages shake off their addiction and start instructing T cells to kill cancer cells, shrinking the tumor. To a similar effect, the endothelial cells stop instructing blood vessels that fed the tumor.”

Dr. Suarez and her colleagues are now testing all these possibilities. The beauty of other microRNAs could be more targeted 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 insights and better ideas to do better research.”