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, they activate factors whose signals cause two important concurrent events. 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 have been programmed to interact with the tumor, they can become addicted, let us say, and transform from their normal function to produce blood vessels to feed and oxygenate the tumor,” explained Dr. Suarez, “they become addicted, on an addiction, and transform from their normal function. Similarly, 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 in the tumor microenvironment. MicroRNAs are small noncoding fragments of RNA that don’t produce protein. “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 coordinate 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 signals from the tumor microenvironment that regulate cells associated with tumorigenesis, 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,” explained Dr. Suarez. “They became addicted, let us say, and transform from their normal function. Similarly, they start helping the tumor to grow.”

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Dr. Suarez and her colleagues are now testing all these possibilities. She believes that other microRNAs could be targets 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.”