As a waste by-product of tumor metabolism, lactic acid has largely been overlooked by cancer scientists. New research at Yale Cancer Center, however, demonstrates that this common chemical compound, produced by the rapid division of neoplastic cells, transforms immune cells called macrophages into aborters of tumor growth. The researchers also identified an enzyme within tumor-associated macrophages (TAMs) that plays a critical role in promoting tumor development. Further, they discovered that removing this single enzyme, called arginase 1 (ARG1), from a macrophage decreased the size of tumors by half.

“That speaks to the important role of macrophages in tumor progression,” said Oscar R. Colegio, MD, PhD, Assistant Professor of Dermatology. “They make up only one to five percent of the cells in our tumor models, yet eliminating one enzyme from that cell type reduces tumor size significantly.”

The research team learned that macrophages are recruited early in the tumor’s development. Through a series of in vitro experiments on macrophages, the scientists detected two proteins critical for tumor growth: a signaling protein called vascular endothelial growth factor (VEGF), and the enzyme arginase 1 (ARG1). Further research revealed that these two proteins used a signaling pathway mediated by a transcription factor called HIF1A (hypoxia-inducible factor 1-alpha). The signals and proteins functioned to convince the macrophages that they were in a state of hypoxia, stimulating the macrophages into frenzied activity that helped the tumor grow.

At that point, they still didn’t know the primary activator. More investigation took them beyond proteins into molecules, and finally to the surprising presence within the tumor bolus and enzymes in tumors models led to the insight that knocking out Arg1 diminished tumor size. Dr. Colegio, all of the links to clinical work caring for recipients of solid organ transplants. To prevent rejection of the transplanted organ, these patients must take strong immunosuppressive drugs, but the drugs cause a one hundred-fold increased risk of melanomas, squamous skin cancer, mostly squamous cell carcinoma. That’s what led Dr. Colegio to study tumor-activated macrophages. He’s now analyzing fresh skin cancers taken from patients, and has found that even in very early stages of skin cancer, the number and density of macrophages is the same as in the later invasive phases. “So we suspect that macrophages help to sustain the immunosuppressed persons,” said Dr. Colegio, “and if they play a role in this, then this may be a target that hasn’t yet been explored in anti-cancer therapies, or in early cancers to try to prevent progression.”

Dr. Colegio is excited by the wider implications of his team’s findings. “The principles, he said, “will likely hold for other tumor types, but not specifically for one cancer type but more broadly across any proliferating tissue.”