How Immune Cells Go Rogue

Oscar R. Colegio, MD, PhD

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 abettors 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 took seven years. Dr. Colegio's postdoctoral research mentor and now main partner throughout the investigation is Ruslan M. Medzhitov, PhD, David W. Wallace Professor of Immunobiology and Investigator of the Howard Hughes Medical Institute. At the beginning, they knew that macrophages are found in all tumors, and that the more of them a tumor contains, the worse the prognosis, which suggests that tumors somehow recruit macrophages and corrupt their normal function as tumor suppressors, turning them into promoters of cancer. Dr. Colegio and his colleagues set out to find the signals that instructed macrophages to become cancer's allies.

"The recruited macrophages act as if there's a wound that won't heal or a tissue that's stressed," explained Dr. Colegio, "so they produce growth factors and vascularize the tumor to restore homeostasis. But that can't happen in neoplasia, so the macrophage ends up feeding the tumor's growth."

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 furious 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 source within the tumor: lactic acid. Experiments in mouse models led to the insight that knocking out Arg1 diminished tumor size.

For Dr. Colegio, all of this links to his clinical work caring for recipients of solid organ transplants. To prevent rejection of the transplanted organ, these patients must take strong immuno-suppressant drugs, but the drugs cause a one hundred-fold increased risk of numerous, aggressive skin cancers, 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 coordinate the invasion process," said Dr. Colegio, "and if they play a role in that, this may be a target that has not yet been exploited in anti-cancer therapies, or in early cancers to try to prevent progression. We could target either the macrophages or use an arginase inhibitor to knock out the enzymatic function that's vital to tumor progression."

Dr. Colegio is excited by the wider implications of his team's findings. The principles, he said, "will likely hold true not just specifically for one cancer type but more broadly across any proliferating tissue."