Medical Xpress

# Arginine restores T-cell ability to target cancer

November 22 2011

In many cases, tumors suppress a patient's immune system in a way that keeps the cancer safe from immune system attack. This is particularly true for patients with glioblastoma, a primary brain tumor that carries a prognosis of only 12-15 months survival after diagnosis.

A study at the University of Colorado Cancer Center, recently published as a featured article in the journal Clinical Cancer Research, shows that treatment with the over-the-counter amino acid arginine may reactivate cancer-fighting T-cells in patients with glioblastoma, thus potentially allowing the immune system to help cleanse the body of cancer.

T-cells are the primary agent responsible for anti-tumor immune responses.

"If you take T-cells from patients with glioblastoma and stimulate them in the lab, they aren't effective (in killing cancer cells)," says lead author Allen Waziri, MD, investigator at the CU Cancer Center, assistant professor of neurosurgery at the University of Colorado School of Medicine. "But when we add back arginine, we restore T-cell function."

In part, function is restored through the activity of neutrophils – an ancient and nonspecific type of white blood cell that kills invaders. After responding to inflammation, neutrophils stop the ongoing immune response. It's as if once they arrive, they consider the infection treated and so suppress any response that exceeds what is needed – a response that if left unchecked would lead to the destruction of healthy tissues.

Neutrophils stop the immune response by secreting an enzyme called arginase. And after they secrete arginase, commonly they die and are excreted by the body. However, in many glioblastoma patients, these neutrophils persist and continue to produce immune-suppressing arginase.

"Persistence of activated neutrophils and increased arginase in the circulation of glioblastoma patients is a fascinating phenomenon, particularly considering that under normal conditions, neutrophils are expected to have an average lifespan of just several hours after activation," he says.

Waziri's group has hypothesized that persistent arginase production from neutrophils suppresses the immune system and keeps cancers from becoming immune targets.

"From one perspective, it appears that glioblastoma is taking advantage of a simple, evolutionarily-ancient method for controlling out-of-control immunity to avoid the specific anti-tumor immune response," Waziri says.

However, there is a step between increased arginase and immune system suppression, and this is where Waziri and colleagues intervene – arginase, in fact, deletes the common amino acid arginine.

T-cells are critically dependent on arginine for activation and function. Therefore, it's not the increase in arginase per se that is responsible for blunting T-cell activity, but rather the resulting lack of arginine that suppresses the immune systems of glioblastoma patients, Waziri's group found.

Waziri and colleagues at the CU Cancer Center recently started a phase 0 clinical trial in newly diagnosed glioblastoma patients to explore

whether a week-long, high-dose course of arginine before cancer surgery can allow an immune system that previously missed cancer cells to recognize and attack them. Waziri and his team will look at the effect of arginine on patients' immune systems as measured by T-cell function, immunological profile, and T-cell infiltration into resected tumor tissue.

"Our overall goal is to improve the efficacy of immunotherapy for glioblastoma," he says. "It's likely that this will require a two-stage approach, including stimulation of the immune system with something like a tumor vaccine while simultaneously targeting the suppressive effects of tumors on the immune system."

With positive results from this initial trial, Waziri hopes to further explore whether longer courses of arginine could help reduce the recurrence of glioblastoma and potentially offer a new strategy for patients with this otherwise incurable disease.

Waziri credits seed grants he has received from the AMC Cancer Fund (a fundraising arm of the CU Cancer Center), he Cancer League of Colorado, and an American Cancer Society Institutional Research Grant for contributing to the preclinical work that has led to this exciting clinical trial.

Provided by University of Colorado Denver