Chronic inflammation can help nurture skin cancer, study shows

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Inflammation, a frontline defense against infection or disease, can help nurture skin cancer, researchers have found. IDO, an enzyme that works like a firefighter to keep inflammation under control, can be commandeered to protect early malignant cells, say Medical College of Georgia researchers studying an animal model of chronic inflammation and skin cancer.

"Inflammation should really help prevent a tumor," says Dr. Andrew Mellor, director of the MCG Immunotherapy Center and Georgia Research Alliance Eminent Scholar in Molecular Immunogenetics. In fact, there is strong evidence that inflammation triggers the immune response. "You want a good immune response; this is what protects you from pathogens," he says. "In this case, it's an unfortunate exploitation by malignant cells."

In a study with Drs. George C. Prendergast and Alexander J. Muller at the Lankenau Institute of Medical Research in Philadelphia, researchers gave mice a single dose of a carcinogen at the same time they began painting a tiny portion of skin with a poison ivy derivative twice weekly for 20 weeks.

IDO quickly became part of the mix, creating a "suppressive" immune response that helped resulting precancerous cells grow into tumors, according to research published online in *Proceedings of the National Academy of Sciences*. When they used the same protocol in a mouse in which IDO had been genetically deleted, tumor development dropped

off dramatically.

The scenario is analogous to chronic sun exposure and skin cancer, says Dr. Mellor, the study's corresponding author. Ultraviolet radiation in sunlight causes malignant skin cells to appear but sun exposure also causes skin inflammation - evidenced by sunburn. The significance of the new study is that the researchers have shown that IDO, or indoleomine 2,3-dioxygenase, may be produced as a part of the inflammatory mix, which could then protect the malignant skin cells. "'Chronic' is the key word," Dr. Mellor says, noting high melanoma rates in Australians, for example, who live deep in the southern hemisphere.

"We have long suspected that IDO is a component of certain kinds of inflammation that create suppression," says Dr. Mellor. IDO's "firefighter" role probably resulted from the body's need to control inflammation in areas such as the gastrointestinal tract. The GI tract is constantly bombarded by food and microbes which could lead to debilitating and deadly inflammation.

"You really set a fire," Dr. Mellor says of inflammation. In fact, the English word inflammation comes from the Latin word inflamatio, which means to set a fire. But instead of helping protect healthy tissue as it does in the GI tract, IDO becomes problematic in cancer.

The latest finding shows IDO has a more important and earlier role than we thought in tumor formation, says Dr. Mellor. He and colleague Dr. David Munn led a research team that 10 years ago showed fetuses use IDO to avoid rejection by the mother's immune system. They and others have subsequently shown that tumors, including melanoma, as well as infectious agents such as HIV also use IDO to escape an immune attack. "IDO favors the tumor: The immune system basically sits back and watches the tumor grow," says Dr. Mellor.

Transplant patients, who require generalized immune inhibitors to keep their transplanted organs, also can be victims of this suppressive inflammation, says Dr. Mellor, noting their high risk of lymphoma after a few years of therapy.

The IDO inhibitor they have been using for years in the lab is now under study in breast cancer patients receiving chemotherapy. Drs. Mellor and Munn also have recruited Dr. Yukai He, cancer vaccine researcher, to MCG to work with them on how vaccines designed to direct an immune attack can work synergistically with the IDO inhibitor.

Source: Medical College of Georgia