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Scientists discover novel tumor suppressor

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La Jolla Institute for Allergy & Immunology researchers studying an enzyme believed to play a role in allergy onset, instead have discovered its previously unknown role as a tumor suppressor that may be important in myeloproliferative diseases and some types of lymphoma and leukemia. Myeloproliferative diseases are a group of disorders characterized by an overproduction of blood cells by the bone marrow and include chronic myeloid leukemia. Lymphoma and leukemia are cancers of the blood.

"PLC-beta 3 is an enzyme, but the function we found was a completely different function that no one knew it had -- as a tumor suppressor," said the La Jolla Institute's Toshiaki Kawakami, M.D., Ph.D., who led the research team. The study, conducted in animal models, could eventually lead to the development of new therapies directed towards controlling this newly discovered cellular mechanism.

Tony Hunter, Ph.D., director of the Salk Institute Cancer Center and a professor in Salk's Molecular and Cell Biology Laboratory, called the finding an "important" step in advancing understanding of blood cancers. "It's very interesting that this molecule acts in this way independently of its enzyme activity," he said. "It's quite an unexpected finding and it definitely has the potential for helping the scientific community understand the mechanisms leading to some types of leukemia."

The findings are being published online today in the journal *Cancer Cell* in a paper entitled "Tumor Suppression by Phospholipase C-beta3 via SHP-1-Mediated Dephosphorylation of STAT5." Researchers from UC

San Diego Cancer Center, University of Alabama and the University of Western Ontario also contributed to the study.

Dr. Kawakami said he and his research team got their first inkling of something unexpected fairly early on in their experiments. "We wanted to better understand the PLC-beta 3 enzyme's possible role as a signaling pathway in asthma and other allergic diseases, so we began working with mice genetically engineered not to have that enzyme," he said. "We noticed that these mice developed a strange phenotype - myeloproliferation and a variety of tumors including lymphomas and some carcinomas."

Dr. Kawakami said this surprising occurrence suggested that PLC-beta 3 acted as a safeguard that inhibited the development of a variety of tumors. He and his team set out to investigate further, choosing to focus specifically on myeloproliferative disease because almost all of the mice with a defective PLC-beta 3 gene eventually developed severe myeloproliferative disease.

The team determined that tumor production hinged on the PLC-beta 3's ability to block the action of STAT5, a transcription factor protein than can switch on many genes known to control cell proliferation, survival and, in the case of blood stem cells, to promote the development of myeloid cells. Myeloproliferative diseases develop when myeloid cells -- which make certain types of white blood cells—become overactive. "In the absence of the PLC-beta 3 protein, STAT5 goes into a state of constant activation, causing the development of abnormal myeloid cells," said Dr. Kawakami. The abnormal cells, which are essentially tumor cells, become overactive and produce too many blood cells leading to myeloproliferative disease, he explained.

The researchers also tested the finding by introducing an inactive form of STAT5 in PLC-beta 3 deficient mice. "This suppressed

myeloproliferative disease in these mice," Dr. Kawakami continued.

Dr. Kawakami said his research team got similar results in tests of human cells from people with Burkitt's lymphoma, an aggressive type of B-cell lymphoma that occurs most often in children and young adults. "Some Burkitt's lymphoma cells have very little PLC-beta 3 expression and have very high levels of STAT5 activity, which is similar to our findings in myeloproliferative disease," he said. "We also have done human cell testing in some other lymphomas and leukemias -- including myeloid leukemia -- indicating that these diseases also use this mechanism (low expression of PLC-beta 3 and high STAT5 activity)."

Dr. Kawakami added that much work still needs to be done. "Our findings need to be explored in other tumors. And, of course, its application in human disease needs further study. But we hope other researchers will be encouraged by our work and that it will prompt not only further analysis of this mechanism's role in various diseases, but attempts to develop drugs that would augment PLC-beta 3 in target cells ."

Source: La Jolla Institute for Allergy and Immunology