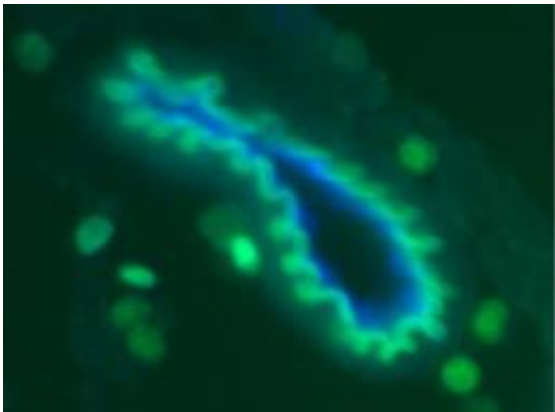


Key found to how tumor cells invade the brain in childhood cancer

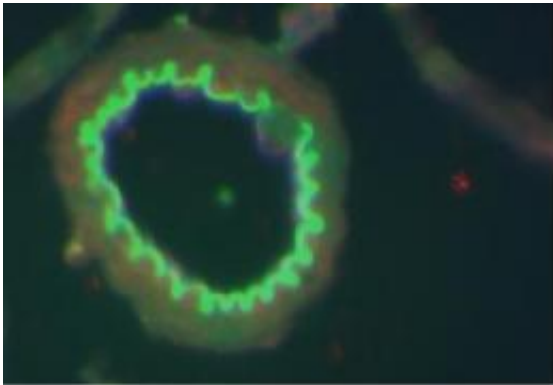
June 17 2009



When two chemokine receptors in the brain interact, leukemic cells (stained green) creep out of a small vein in the membrane covering the brain of a mouse and enter the cerebrospinal fluid. The chemokine CCL19, which is in the endothelium lining the vein, is stained blue in this immunofluorescent image. Credit: NYU School of Medicine

Despite great strides in treating childhood leukemia, a form of the disease called T-cell acute lymphoblastic leukemia (T-ALL) poses special challenges because of the high risk of leukemic cells invading the brain and spinal cord of children who relapse. Now, a new study in the June 18, 2009, issue of the journal *Nature* by scientists at NYU School of Medicine reveals the molecular agents behind this devastating infiltration of the central nervous system. The finding may lead to new drugs that block these agents and thus lower the risk of relapse.

T-ALL, a blood-borne cancer in which the bone marrow makes too many lymphocytes, or [white blood cells](#), strikes several hundred children and adolescents in the U.S. annually. While greater than 90% percent go into remission through a combination of chemotherapy and radiation, up to one third of this group end up relapsing. These patients are at particular risk for [tumor cells](#) to invade the brain and spinal cord, and to prevent this all patients receive chemotherapy injections into the central nervous system and in some cases cranial irradiation—approaches that cause dangerous side effects, including secondary tumors and potentially permanent cognitive and developmental deficits.



When the interaction between the two chemokine receptors is inhibited, there is no infiltration of the brain by green-stained leukemic cells. Credit: NYU School of Medicine

“In general, T-cell acute lymphoblastic leukemia is treatable with chemotherapy and radiation,” said Ioannis Aifantis, PhD, associate professor of pathology and co-director of the Cancer Stem Cell Program at the NYU Cancer Institute, who led the new study. “But you have a very high rate of relapse. And after the relapse, it is not treatable because the cancer occurs in tricky places like the central nervous system,” said Dr. Aifantis, who is also an Early Career Scientist at the Howard Hughes

Medical Institute.

“We are very proud of this research and very excited about the potential implications for new therapeutic approaches to prevent or reduce the spread of leukemic cells into the central nervous system,” said Vivian S. Lee MD, PhD, MBA, the vice dean for science, senior vice president and chief scientific officer of NYU Langone Medical Center.

In the new study, Dr. Aifantis and his colleagues found that a key protein receptor embedded on the outer surface of leukemic cells is responsible for infiltrating the brain and spinal cord. “What we have found is that leukemic cells over-express this receptor.” said Dr. Aifantis, “If you knock out this receptor, these cells will not go to the brain under any circumstances.”

Previous research had strongly implicated a famous gene regulator called Notch1 in the progression of T-ALL. The Notch1 gene (a mutated version gives fruit flies notched wings) is an oncogene, or cancer-causing gene, in humans. Certain kinds of mutations in this gene have been found in nearly half of all T-ALL patients, and current estimates suggest that the gene’s regulatory influence might be implicated in nearly 90 percent of all T-ALL cases.

For their new study, Dr. Aifantis and his colleagues first introduced overactive forms of Notch1 into mice. As a result, the mice developed leukemia and the leukemic cells efficiently infiltrated the inner layers of the membrane covering the brain. “What happens is that the leukemic cells get into the cerebrospinal fluid that protects our brain and spine, where they fill up the space and they can affect brain function, either by secreting chemicals and toxic factors or even by simple pressure,” Dr. Aifantis said.

His team then examined an array of other mouse genes to identify

candidates that might fall under the regulatory spell of Notch1 to promote the brain and spinal cord infiltration. The screen revealed a promising gene for a protein named CCR7, which is embedded on the surface of lymphocytes. This chemokine receptor, as it's known, normally senses and responds to small chemical attractants called chemokines, which act like recruitment signals for lymphocytes to converge on a specific site during the body's response to infection or injury. In leukemia, however, these lymphocytes proliferate abnormally.

CCR7 was already known as a key player in normal lymphocyte migration and as a binding partner of two chemokines named CCL19 and CCL21. Previous studies had implicated these protein interactions in the metastasis of other tumors such as melanomas and breast cancers. Dr. Aifantis's team also discovered that the gene for CCR7 was overactive in four of five T-ALL cell lines derived from human patients, bolstering suspicions that it played a central role in the disease. Conversely, a mutation that knocked out Notch1 also led to dramatically reduced CCR7 levels.

To characterize CCR7's potential role in T-ALL, the researchers used two sets of mice: one in which the receptor was turned on, and a second in which it was turned off. When the team delivered an identical number of human-derived leukemic cells to both sets of mice, those with the CCR7 chemokine receptor turned off lived almost twice as long. Using bioluminescent imaging, the researchers quickly understood why: animals with the active CCR7 receptor had many more tumors. Tellingly, the T-ALL cells had infiltrated the brain and spinal cord of those mice.

Further experiments suggested that when healthy mice received leukemic cells in which the gene for CCR7 had been turned off, the cells could not migrate to the brain even though they reached other body tissues. As a result, the mice survived significantly longer than

counterparts with an active copy of the gene. On the other hand, introducing a normal version of the same gene to mice otherwise lacking it was enough to recruit leukemic cells to the brain and spine.

“We wanted to determine whether CCR7 by itself was sufficient for entry into the central nervous system and that’s what this experiment shows,” Dr. Aifantis said. “By changing one specific gene, you now have your function back.”

Finally, the researchers identified the small protein that acted as the “come hither” signal for the CCR7 protein receptors. One candidate, CCL21, was undetectable in leukemic mice. But a second, CCL19, appeared in tiny veins of the brain near the infiltrating tumor cells. When the researchers introduced [leukemic cells](#) carrying a gene for CCR7 to mice that naturally lacked the CCL19 chemokine, the mice survived longer, suggesting that their increased life spans might be due to a disrupted interaction of the two proteins. The [leukemic cells](#) had no trouble infiltrating other tissue like the lymph nodes, but were completely incapable of infiltrating the brains of CCL19-deficient mice, the researchers report.

“Perhaps there are antibodies or small molecules that can block the interaction between these two proteins or reduce their interactions,” Dr. Aifantis said, “and hopefully that could be used as a type of prophylactic treatment to prevent a relapse in the central [nervous system](#) among patients who have already been treated for leukemia.” Such a treatment, he said, could prove a good alternative to the intensive and often poorly tolerated radiation and chemotherapy now used to try to block such a relapse.

Source: NYU Langone Medical Center / New York University School of Medicine

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